EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2018
EMA/556923/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RXULTI

International non-proprietary name: brexpiprazole

Procedure No. EMEA/H/C/003841/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

5-HT	Serotonin (5-hyrodoxytryptamine)
$5\text{-HT}_{1A/1B/1D}$	Serotonin $5\text{-HT}_{1A/1B/1D}$
$5\text{-HT}_{2A/2B/2C(s23c)/2C(vsv)}$	Serotonin $5\text{-HT}_{2A/2B/2C}$
$5\text{-HT}_{3/5A/6/7/7A}$	Serotonin $5\text{-HT}_{3/5A/6/7/7A}$
ADR	Adverse drug reaction
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotrasferase
APO	Apomorphine
ARI	Aripiprazole
ASMF	Active Substance Master File
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{∞}/AUC_{inf}	Area under the concentration-time curve from time zero to infinity (inf= ∞)
AUC_t	Area under the concentration-time curve calculated to the last observable concentration at time t
AUC_{tau}	Area under the plasma concentration-time curve during a dosing interval (tau [τ])
BARS	Barnes Akathisia Rating Scale
BE	Bioequivalence
BREX	Brexpiprazole
CAR	Cariprazine or conditioned avoidance response
CDP	Clinical development program
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity of Illness
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Apparent total body clearance of drug from plasma
CL/F	Apparent total clearance of drug from plasma after extravascular administration
C_{max}	Maximum (peak) plasma drug concentration
CNS	Central nervous system
CoA	Certificate of analysis
CPK	Creatine phosphokinase
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	Controlled release
CSR	Clinical Study Report
CYP	Cytochrome P450
DoE	Design of experiments
EC	European Commission
EC_{50}	Concentration of drug producing 50% of the maximum effect

EC_{80}	Concentration of drug producing 80% of the maximum effect
ECG	Electrocardiogram
EM	Extensive metabolizer
EMA	European Medicines Agency
EMEA	Europe, Middle East, and Africa
EPS	Extrapyramidal symptoms
EU	European Union
FAERS	FDA Adverse Event Reporting System
FAS	Full analysis set
FDA	US Food and Drug Administration
F	Bioavailability
GC	Gas Chromatography
f_u	Fraction of unbound drug in plasma
GMR	Geometric mean ratio
GVP	Good pharmacovigilance practices
H_1	Histamine 1
HCD	Historical control data
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
IC_{50}	Half maximal inhibitory concentration ICH
IMP	Investigational medicinal product
IR	Infrared
IRR	Incidence rate ratio
ITT	Intent to treat
K_i	Inhibition constant
KF	Karl Fischer titration
LOCF	Last observation carried forward
LS	Least squares
LSMD	Least squares mean difference
LTSS	Long-term stability studies
LUR	Lurasidone
M_1	Muscarinic-1 cholinergic
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MRHD	Maximum human recommended dose
MTD	Maximum tolerated dose
N (or n)	Number
NA	Not applicable or not available
ND	New Drug Application
NMR	Nuclear Magnetic Resonance
NMS	Neuroleptic malignant syndrome
NNH	Number needed to harm
NOAEL	No-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development

OLA	Olanzipine
PASS	Post-authorisation safety study
PANSS	Positive and Negative Syndrome Scale for schizophrenia
PCP	Phencyclidine
PCR	Potentially clinically relevant
pc-VPC	Prediction-corrected Visual Predictive Check
PDA	Photo diode array detector
PET tomography	Positron emission
PH	Potential of hydrogen
Ph Eur	European Pharmacopeia
PK	Pharmacokinetic
PM	Poor metabolizer
PO	Oral
PRAC	Pharmacovigilance Risk Assessment Committee
PSP	Personal and Social Performance scale
PT	Preferred term
PVC	Polyvinyl chloride
RMP	Risk Management Plan
QbD	Quality bu design
QC	Quality control
QUE	Quetiapine
QTc	Heart-rate corrected QT interval
QTcB	QTc interval, heart-rate corrected using Bazett’s formula
QTcF	QTc interval, heart-rate corrected using Fridericia's
formula QTcI correction RH	QTc interval, heart-rate corrected using individual Relative humidity
QTTP	Qualiy target product profile
RIS	Respiradone
RMM	Risk minimisation measures
RMP	Risk management plan
SAS	Simpson-Angus Scale
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SmPC	Summary of Product Characteristics
S-QoL	Schizophrenia-Quality of Life Questionnaire
$t_{1/2}$	Elimination half-life
TD	tardive dyskinesia
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
T_{max}	Time of maximum (peak) concentration
TQT	Thorough QT
TSE	Transmissible Spongiform Encephalopathy
ULN	Upper limit of normal

US	United States
USPI	United States Prescribing Information
UV	Ultraviolet
V_C/F	Apparent central volume of distribution
V_d/F	Apparent volume of distribution
VPC	Visual Predictive Check
V_p/F	Apparent peripheral volume of distribution
Vs	Versus
VTE	Venuous thrombeoembolism
WHO Organization	World Health
w/v	Weight per volume
XR	Extended release
XRPD	X-ray powder-diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Otsuka Pharmaceutical Europe Ltd submitted on 28 February 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for RXULTI, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2013.
The applicant applied for the following indication "RXULTI is indicated for the treatment of schizophrenia in adult patients."

The legal basis for this application refers to:
Article 8.3 of Directive 2001/83/EC - complete and independent application
The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0234/2016 on the granting of a product-specific waiver and on the agreement of a paediatric investigation plan (PIP).
At the time of the submission of the application, the PIP P/0234/2016 was not yet completed, as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance brexpiprazole contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMEA/CHMP/SAWP/261256/2011	14 April 2011	clinical
EMEA/CHMP/SAWP/451459/2012	19 July 2012	clinical
EMEA/CHMP/SAWP/352896/2013	27 June 2013	clinical

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Daniela Melchiorri
Co-Rapporteur: Greg Markey

The application was received by the EMA on	28 February 2017
The procedure started on	23 March 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 June 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	9 June 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 June 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 January 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	28 February 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 March 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 March 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 April 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 May 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to RXULTI on	31 May 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Schizophrenia is a life-long psychiatric disorder. The cardinal symptoms fall into 3 domains: positive symptoms such as delusions and hallucination, negative symptoms such as lack of drive and social withdrawal, and cognitive symptoms such as problems with attention and memory.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Schizophrenia is a severely debilitating mental illness that affects 0.7% of the population worldwide. Moreover, an analysis has estimated that the annual prevalence of diagnosed schizophrenia in Europe is 0.31 % and 0.51 % in North America. The prevalence of the disorder seems to be equal in males and females, although the onset of symptoms occurs at an earlier age in males than in females. Males tend to experience their first episode of schizophrenia in their early 20s, whereas women typically experience their first episode in their late 20s or early 30s. Research into a possible link between the geography of birth and the development of schizophrenia has provided inconclusive results.

2.1.3. Biologic features, aetiology and pathogenesis

Biological theories of schizophrenia have focused on genetics and, structural and functional abnormalities in the brain. Family, twin and adoption studies indicate an important genetic contribution to the aetiology of schizophrenia. Most studies seem to agree that many patients appear to suffer from a disorder of early brain development. Methodological problems have limited studies into the possible aetiology of schizophrenia but many of these problems are being overcome by modern technology. Clinically, schizophrenia is heterogeneous and this may point to heterogeneous aetiology. It seems that genetics, neurodevelopmental problems, neurochemistry and abnormal connectivity, as well as psychosocial stressors probably all contribute to developing the typical clinical pictures of schizophrenia.
Abnormalities in neurotransmission have provided the basis for theories on the pathophysiology of schizophrenia. Most of these theories focus on either an excess or a deficiency of neurotransmitters including dopamine, serotonin, and glutamate. Other theories implicate aspartate, glycine, and gamma-aminobutyric acid (GABA) as part of the neurochemical imbalance of schizophrenia.
Abnormal activity at dopamine receptor sites (specifically D2) is thought to be associated with many of the symptoms of schizophrenia. Four dopaminergic pathways have been implicated. The nigrostriatal pathway originates in the substantia nigra and ends in the caudate nucleus. Low dopamine levels within this pathway are thought to affect the extrapyramidal system, leading to motor symptoms. The mesolimbic pathway, extending from the ventral tegmental area (VTA) to limbic areas, may play a role in the positive symptoms of schizophrenia in the presence of excess dopamine. The mesocortical pathway extends from the VTA to the cortex. Negative symptoms and cognitive deficits in schizophrenia are thought to be caused by low mesocortical dopamine levels. The tuberoinfundibular pathway projects from the hypothalamus to the pituitary gland. A decrease or blockade of tuberoinfundibular dopamine results in elevated prolactin levels and, as a result, galactorrhea, ammenorrhea, and reduced libido.

The serotonin hypothesis for the development of schizophrenia emerged as a result of the discovery that lysergic acid diethylamide (LSD) enhanced the effects of serotonin in the brain.1 Subsequent research led to the development of drug compounds that blocked both dopamine and serotonin receptors, in contrast to older medications, which affected only dopamine receptors. The newer compounds were found to be effective in alleviating both the positive and negative symptoms of schizophrenia.
Another theory for the symptoms of schizophrenia involves the activity of glutamate, the major excitatory neurotransmitter in the brain. This theory arose in response to the finding that phenylciclidine and ketamine, two noncompetitive NMDA/glutamate antagonists, induce schizophrenia-like symptoms. This, in turn, suggested that NMDA receptors are inactive in the normal regulation of mesocortical dopamine neurons, and pointed to a possible explanation for why patients with schizophrenia exhibit negative, affective, and cognitive symptoms.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Schizophrenia is a severely debilitating psychotic disorder characterized by positive, negative and cognitive symptoms. Positive symptoms are the most easily identified and these are: delusions, hallucinations, and abnormal motor behaviour in varying degrees of severity. Negative symptoms are more difficult to diagnose but are associated with high morbidity as they disturb the patient's emotions and behaviour. The most common negative symptoms are diminished emotional expression and avolition (decreased initiation of goal-directed behaviour). Patients may also experience alogia and anhedonia. Cognitive symptoms are the newest classification in schizophrenia. These symptoms are nonspecific; therefore, they must be severe enough for another individual to notice them. Cognitive symptoms include disorganized speech, thought, and/or attention, ultimately impairing the individual's ability to communicate.
A patient usually gradually recovers from the first episode of schizophrenia. However, relapses are common, and pattern of the illness during the first 5 years indicates generally the course. In general, deterioration in the patient's baseline functioning after each relapse happens. Positive symptoms tend to ease with time, but the socially debilitating negative and deficit symptoms may increase and become more severe. Only 10-20% of schizophrenia patients have been described to achieve a good outcome. It has been estimated that 20-30% continue to experience moderate symptoms and 40-60% remain significantly impaired. This means that patients with schizophrenia often have great difficulties in integrating in society and to normal life by impairing functioning, for example through the loss of an acquired capability to earn a livelihood or the disruption of studies. In addition, comorbidity with other somatic diseases, such as obesity, cardiovascular diseases and diabetes mellitus, as well as with substance abuse is common in patients with schizophrenia. People with schizophrenia have a 40-60% higher rate of dying prematurely than general population due to physical health problems and suicide.

2.1.5. Management

Antipsychotic medications are the mainstay treatment for schizophrenia in addition to psychosocial interventions. Antipsychotics diminish symptoms and reduce relapse rates. Antipsychotics have a wide variety of pharmacological properties but they all have a capacity to antagonize postsynaptic dopamine receptors in the brain.
In the event of an acute psychotic episode, drug therapy should be administered immediately. During the first seven days of treatment, the goal is to decrease hostility and to attempt to return the patient to normal functioning (e.g., sleeping and eating). At the start of treatment, appropriate dosing should be titrated based on the patient's response.

Treatment during the acute phase of schizophrenia is followed by maintenance therapy, which should be aimed at increasing socialization and at improving self-care and mood. Maintenance treatment is necessary to help prevent relapse. The incidence of relapse among patients receiving maintenance therapy, compared with those not receiving such therapy, is 18% to 32% versus 60% to 80%, respectively. Drug therapy should be continued for at least 12 months after the remission of the first psychotic episode.
Second-generation (atypical) antipsychotics (SGAs) are the agents of choice for first-line treatment of schizophrenia. Clozapine is not recommended because of its risk of agranulocytosis. SGAs are usually preferred over first-generation (typical) antipsychotics (FGAs) because they are associated with fewer extrapyramidal symptoms. However, SGAs tend to have metabolic side effects, such as weight gain, hyperlipidemia, and diabetes mellitus. These adverse effects can contribute to the increased risk of cardiovascular mortality observed in schizophrenia patients.

About the product

Brexpiprazole is 7-[4-(4-Benzo[b]thiophen-4-ylpiperazin-1-yl) butoxy]quinolin-2(1H)-one, a chemical entity discovered by Otsuka Pharmaceutical Co., Ltd. and is being developed jointly with H. Lundbeck A/S.
Under the name of Rexulti, brexpiprazole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg was approved by the FDA on 07/10/2015 for the treatment of major depressive disorder as an adjunctive therapy to antidepressants and for the treatment of schizophrenia.
Brexpiprazole mode of action, as claimed by the Applicant is:

i. partial agonist activity at serotonergic 5-HT1A and at dopaminergic D2 receptors
ii. antagonist activity at serotonergic 5-HT2A receptors, with similar high affinities at all of these receptors (Ki: 0.1-0.5 nM);
iii. antagonist activity at noradrenergic α1B/2C with affinity in the same sub-nanomolar Ki range (Ki: 0.2-0.6 nM);
iv. a broad spectrum of binding affinities and actions on several other central monoaminergic receptor subtypes.

Development programme/compliance with CHMP guidance/scientific advice

The development program for brexpiprazole does not entirely comply with EMA Guidelines. First, the design of the dose response study is a multiple flexible doses study rather than a fixed dose.
In this regard, the EMA Guidelines for the investigation of products for the treatment of schizophrenia state:
[…] dose-response relationships need to be established in clinical trials using validated efficacy endpoints. The minimum effective dose and the dose at which best efficacy is obtained should be established. Flexible dose designs are unsuitable to provide this information and therefore designs with multiple fixed doses and a placebo control are required. It is preferred to make direct dose comparisons of multiple doses in a single study. Dose response is typically established in short-term studies, and this information serves as a basis for dose selection in both additional short-term phase 3 studies and the longer term maintenance study. It is strongly recommended to establish the dose-response of the investigational drug prior to the start of confirmatory trials (Phase 3) as the use of inadequately justified doses may hamper interpretation of the latter trials.
The EMA gave 3 Scientific Advice (EMA/CHMP/SAWP/261256/2011, EMA/CHMP/SAWP/451459/2012, EMA/CHMP/SAWP/352896/2013) on clinical development of brexpiprazole in the treatment of schizophrenia and agitation in patients with dementia of the Alzheimer's type.

The EMA scientific advice issued in 2011 (EMEA/H/SA/2104/1/2011), warned Applicants on uncertainties around the dose and on the need to establish a clear dose-response prior to start a phase 3 trial. A fixed dose finding study was suggested.
In addition, the Applicant conducted four pivotal studies three of which were placebo controlled.
EMA Guidelines for the investigation of products for schizophrenia in this regard state that:
Crossover designs are unsuitable for trials in patients with schizophrenia. Confirmatory trials should be double-blind, randomised, parallel group trials.
The study protocol should provide a justification of the choice of the active comparator – this would normally be an active comparator with proven efficacy and, if from a similar class, a similar clinical pharmacological profile to the test product. If the product is the first in its class an appropriate active comparator would be a product licensed in the target indication and population or, if there is no suitable licensed product, a medicinal product recognised as the "gold standard" for the target indication and population in clinical practice should be chosen as a suitable active comparator.
If the aim of the study is to demonstrate non-inferiority to an active comparator, then a three-arm study of placebo, test product and active comparator is recommended (see also section 4.4.3.7.). Superiority to placebo should be demonstrated in order to ensure assay sensitivity of the study.
Alternatively, a two-arm study of test and active comparator would be acceptable provided superiority of the test product over an appropriately justified active comparator was demonstrated.
Having all this above considered the most logical comparator in a fixed dose study (or studies) should have been aripiprazole.
In addition, advice was given on the planned bioequivalence study between oral tablet and the future oral solution.

General comments on compliance with GMP, GLP, GCP

GMP:
A valid Qualified Person declaration, confirming that the active substance manufacturing sites operate in compliance with current guidelines on Good Manufacturing Practice for active substances, has been provided.
Valid GMP certificates have been provided for the batch releasers and manufacturers of the drug product.

GLP:
All safety/toxicological *in vitro* and *in vivo* studies on brexpiprazole and on its main metabolite were performed between 2006 and 2012 in Japanese test facilities. Studies were declared to be GLP compliant: since Japan joints the mutual acceptance of data, this can be considered acceptable.

GCP:
The clinical trials conducted to support this submission were performed in accordance with the principles of Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), and those carried out within the European Community met the ethical requirements of Directive 2001/20/EC. Clinical trials carried out outside the European Union were conducted in accordance with the principles of GCP and the ethical requirements equivalent to the provisions of Directive 2001/20/EC.

In light of the GCP compliance issues identified at an investigator site in Romania, the County Hospital Arad, The Applicant provided

- An overview of the number of patients enrolled at the above mentioned site, (County Hospital, Arad, Romania)

- The percentage of patients enrolled at the above mentioned site vs. the worldwide total number of patients enrolled.

For each pivotal clinical trial included in the above mentioned applications an assessment of the impact of the potential exclusion of the patients enrolled at the site in Arad, Romania, on the efficacy and safety data submitted in support of each application.

Table 1: Brexiprazole Schizophrenia Trials – Subjects Enrolled at Dr Podea's Site (Arad Romania) by Trial

Table 1: Brexpiprazole Schizophrenia Trials - Subjects Enrolled at Dr. Podea's Site (Arad, Romania) by Trial					
Study Code	**EudraCT Number**	**Romanian Sites Included (Yes/No)**	**If Yes, County Hospital Arad Site Included?**	**Total Number of Patients Enrolled in Romania/ Worldwide Total No. of Patients**	**Total Number of Patients Enrolled at the County Hospital Arad**
331-10-231	2011-002538-38	Yes	Yes	109/636	12
331-10-232	2011-005766-38	Yes	Yes	Enrolled in Stabilization Phase: 57/464 Randomized: 16/202	Enrolled in Stabilization Phase:13 Randomized: 4
331-10-237	2011-002514-37	Yes	Yes	80/1044	11
14644A	2012-002252-17	Yes	Yes	38/468	12

Only a small number of patients from Dr. Podea's site participated in the brexpiprazole schizophrenia clinical program. Excluding these patients from the efficacy reanalysis did not have any impact and the conclusion on the efficacy analyses remains the same. Similarly, review of all Treatment Emergent Adverse Events (TEAEs) at the site including narratives for all Immediately Reported Events and given the low number of subjects at the site in comparison to the cumulative safety database, it is concluded that the safety profile of brexpiprazole remains unchanged.

Type of Application and aspects on development

- Legal basis
  The present Marketing Authorisation Application (MAA) for RXULTI falls under optional scope (Article 3(2a) of Regulation (EC) No 726/2004) since the active substance (brexpiprazole) is a new active substance not yet authorised in a medicinal product by a competent authority or by the European Union, in the treatment of schizophrenia in adult patients.
  This is an independent full MAA under article 8(3) of Directive 2001/83/EC with complete administrative, quality, pre-clinical and clinical data. Justification for the claim of new active substance status was provided.

- Accelerated procedure
  Not requested

- Conditional approval
  Not requested

- Exceptional circumstances
  Not requested

- Biosimilar application

NA

- 1 year data exclusivity
  NA

- Significance of paediatric studies

A Pediatric Investigation Plan (PIP) was issued (Decision Number P/0234/2016) including waiver for population from birth to 13 years of age since the disease condition does not occur in the specified paediatric subset. A PIP COMPLIANCE VERIFICATION (EMEA-C2-001185-PIP01-11-M03) was agreed including 3 clinical studies to be completed by December 2022.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg of brexpiprazole as active substance.
Other ingredients are:
Tablet core: lactose monohydrate, maize starch, microcrystalline cellulose, low-substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate, and purified water.
Tablet coat: hypromellose, talc, titanium dioxide, iron oxide E 172 (yellow, red, black for 0.25 mg tablets),
iron oxide E 172 (yellow, red for 0.5 mg tablets), iron oxide E 172 (yellow for 1 mg tablets), iron oxide E 172 (yellow, black for 2 mg tablets), and iron oxide E 172 (red, black for 3 mg tablets).
The product is available in aluminium/PVC blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of brexpiprazole is 7-{4-[4-(1-Benzothiophen-4-yl) piperazin-1-yl] butoxy} quinolin-2(1*H*)-one corresponding to the molecular formula $C_{25}H_{27}N_3O_2S$. It has a relative molecular mass of 433.57 g/mol and the following structure:

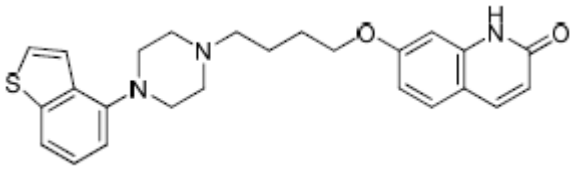


Figure 1: active substance structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis, ultraviolet absorption (UV) spectrum, infrared absorption spectrum (KBr pellet method), nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry.
The active substance is a white to off-white crystal or crystalline powder, it is not hygroscopic, and it is practically insoluble in water (0.0024 mg/mL) and its solubility is pH dependent.
Brexpiprazole has a non - chiral molecular structure.
Polymorphism has not been observed for the active substance.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. Brexpiprazole is synthesized in 5 main steps using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in polyethylene bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended, closed with a tie-wrap, which is then packaged in another polyethylene bag and closed with a tie-wrap. The double-polyethylene bag is stored in a fibre drum with a securely fitting lid.

Specification

The active substance specification includes tests for description (visual), identification (UV, IR), impurities (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.), assay (HPLC), particle size distribution (Ph. Eur.). Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 6 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from one of the proposed manufacturers stored in the intended commercial package under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Bulk container stability studies are in progress for three pilot-scale batches of brexpiprazole manufactured at the second proposed manufacturing site. Samples will be stored in the intended commercial package under long term conditions and for up to 6 months under accelerated conditions. The stability protocols and packages for the batches made at this manufacturing site are the same as those for the first manufacturing site.

The following parameters were tested: description, identification, melting point, drug-related impurities, residual solvents, water content, assay, and particle size distribution. The analytical methods used were the same as for release and are stability indicating.

Little or no variability was observed for all tested parameters for all batches manufactured by both sites under both accelerated and long term conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. No significant changes were observed to any of the tested parameters. The photostability study confirms that brexpiprazole is not light sensitive.

Results under stressed conditions at 50 °C (closed amber glass bottle), 25 °C / 90% RH (open Petri dish), and 40 °C / 75% RH (open Petri dish) for 3 months and under white fluorescent/near ultraviolet for 600 hours were also provided for 1 pilot scale batch from one manufacturing site. The stability results under stress conditions demonstrate the stability of the active substance to heat and humidity.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period without specific storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

RXULTI is presented as light brown (0.25 mg), light orange (0.5 mg), light yellow (1 mg), light green (2 mg), light purple (3 mg), and white (4 mg) round, shallow, convex, bevel-edged film-coated tablets, debossed with BRX and 0.25, 0.5, 1, 2, 3, or 4 respectively on one side.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except the coating agents, which are well-known mixtures compliant with in house standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.
The tablet dosage form was chosen as a convenient delivery system for the oral route of administration. The formulation development of brexpiprazole is based on prior knowledge and systematic enhanced approaches.
A quality target product profile (QTPP) was established based on previous experience and potential critical quality attributes (CQAs).
The active substance attributes and excipient attributes were assessed to understand their influences on potential CQAs.Design of experiments (DoEs) were carried out to evaluate and understand the formulation and granulation process factors. The dissolution test method for brexpiprazole tablets was designed so that it could distinguish between differences in formulation and manufacturing process variants.
All strengths of the tablets used in clinical trials and the proposed commercial tablets were the same shape, 6 mm in diameter and 93 mg of tablet weight, and no changes were made except the film-coating components and debossing. All clinical tablets were the same red colour while the proposed commercial tablets differ in colours for strength differentiation.

The finished product is manufactured by wet granulation method using a high shear mixer granulator. There have been no significant changes in the manufacturing process from phase 1 clinical trial tablets to the proposed commercial tablets except for the drying method and an increase of batch size.
The primary packaging is aluminium/PVC blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The granules for brexpiprazole tablets are manufactured by a wet granulation process using a high shear mixer granulator. The wet granules are dried, sized, blended and mixed with lubricant, following by compression into tablets with a rotary tablet press and film-coating. The process is considered to be a non-standard manufacturing process.
Validation of 6 commercial batches (one per strength) has been performed. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description/appearance (visual), identification (HPLC-PDA), impurities/degradation products,

uniformity of dosage units by content uniformity (Ph. Eur.), dissolution, assay (HPLC), and microbial limit test (Ph. Eur.).
The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product
Stability data from 3 commercial scale batches per strength of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.
Samples were tested against the same specifications as for release. The analytical procedures used are stability indicating.
No significant changes to any of the measured parameters were observed when the finished product was stored under long term or accelerated conditions.
In addition, photostability studies were conducted on loose tablets, and on tablets packaged in PVC/aluminium foil blisters. One representative batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of the photostability studies indicate theproductis no sensitive to light.
Open dish studies were conducted on loose tablets using one representative batch of each strength over periods of 3 months. The data from the open dish studies demonstrate the stability of brexpiprazole tablets to humidity.
A freeze-thaw cycling study was performed on the tablets packaged in PVC/aluminium foil blisters or double polyethylene bags/fibre drums using two representative lots of each strength, stored for 10 hours at –20 ºC and 10 hours at 40 ºC, with a complete cycle every 24 hours for 2 weeks. The data indicate that the product is not affected by temperature excursions and may be shipped through normal distribution channels.

An elevated temperature (50 ºC) stress study was carried out on one representative batch of tablets of all strengths, packaged in PVC/aluminium foil blisters over a period of 3 months. The data from elevated temperature study demonstrate the stability to heat.
Stability studies were also conducted on two production scale batches of bulk tablets of each strength packaged in the proposed double polyethylene bags/fibre drum shipping container, stored at 30 ºC/65% RH for 12 months. Since no significant changes were observed at any of the test points, a 12 month holding period has been assigned for the bulk tablets in double polyethylene bags/ fibre drums when stored below 30 ºC.

Based on available stability data, the proposed shelf-life of 36 months without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.
The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacological profile of brexpiprazole (OPC-34712) was characterised in several *in vitro* receptor, transporter, and enzyme assays, both in binding studies and in relevant functional tests. In most of the studies, the *in vitro* brexpiprazole features were compared to those of aripiprazolefrom the same MAH approved for the treatment of schizophrenia (Abilify).

Additionally, *in vitro* binding affinities and functional effects of the major metabolite, the S-oxide of benzothiophene moiety of brexpiprazole DM-3411 (Lu AF59163), were determined for a broad range of receptors.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Dopaminergic receptors
In human receptor binding assays, brexpiprazole showed the following affinity (Ki nM) to the D receptor subtypes tested: D2L (0.3) >D3 (1.1)> D4 (6.3)>D1 (160). High affinity was demonstrated to D2L and D3, while moderate and very low affinities were shown towards D4 and D1. Binding affinity of brexpiprazole to D2L and D3 was quite similar than that of aripiprazole (0.87 and 1.6, respectively): both receptors are known to play a role in the pathophysiology of schizophrenia.
Functional assays were only performed for D2L and D3 that, together with D4, are receptors coupled to inhibitory G-proteins. On D2L, brexiprazole inhibited the cAMP accumulation more potently than aripiprazole (nM EC50=4.0 vs 5.6) but with a lower intrinsic activity relative to dopamine (Emax %=40 vs 60). A similar behavior was observed when the calcium mobilization assay was used, even if this latter test was much less sensitive than cAMP assay.
Also on D3, brexpiprazole inhibited the cAMP accumulation more potently than aripiprazole (nM EC50=2.8 vs 5.9) with a lower intrinsic activity relative to dopamine (Emax % =15 vs 28).

Based on these *in vitro* results, OPC-34712 could be classified as a partial agonist for dopamine D2L and D3 receptors with lower (approx 1.5-1.8 fold for D2L and D3, respectively) intrinsic activity compared to aripiprazole and an higher potency. This can translate into an *in vivo* brexpiprazole behavior/features closer to that of traditional antagonist drugs than aripiprazole. D3 weak partial agonism could improve cognitive and emotional symptoms.

Serotoninergic receptors

In human receptor binding assays, brexpiprazole showed the following affinity (Ki nM) to the 5HT receptor subtypes tested: 5HT1A (0.12-0.15) >5HT2A (0.47)> 5HT2B (1.9)> 5HT7 (3.7)> 5HT7A (9.5)> 5HT2CS23C (12) >5HT1B (32) =5HT2C (VSV) (34) > 5HT6 (58) > 5HT5A (140).
High affinity was demonstrated to 5HT1A, 2A, 2B, 7 while moderate affinity was shown towards 5HT7A, 2CS23C, 1B, 2C (VSV) and 6, and very low affinity towards 5HT5A. Binding affinity of brexpiprazole was generally higher than that of aripiprazole: 6- to 10-fold higher to 5HT1A (0.88 in brain tissue -superior frontal cortex- and 1.3 in cloned receptor), 10-fold higher to 5HT2A (4.7), 3-fold higher to 5HT2C (VSV) and to 5HT7A.
In functional assay measuring [35S]-GTPγS binding to cells expressing cloned 5-HT1A receptors, brexpiprazole acted as potent (EC50=0.49 nM) partial agonist leading to increase of binding with an Emax of 60% relative to serotonin: the maximum intrinsic activity vs serotonin was slightly lower than that of aripiprazole (73%) even if brexpiprazole was > 4-fold potent (nM EC50 0.49 vs 2.1). The same behavior was observed when the superior frontal cortex receptor (not known whether it was from healthy or schizophrenic subject) was tested. However, at comparable Ki values, in superior frontal cortex absolute EC50 and Emax values were much lower than that found in the cloned assay in HeLa cells (33% vs 60% in HeLa cells). It is noted that in superior frontal cortex the intrinsic activity for brexpiprazole was calculated vs the agonist compound 8-OH-DPAT and not vs setotonin that reached an higher maximal effect (approx. 120% vs 90% 8-OH-DPAT): this further overstimates the value.
Brexpiprazole showed to be a moderate antagonist towards 5HT2A (IC50=6.5 nM) > 2B (IC50=14 nM) in functional assay measuring serotonin-induced production of inositol monophosphate (IP1): no comparison with aripiprazole is possible since this latter was not tested.
Brexpiprazole showed to be a weak antagonist towards 5HT6 and 7A in functional assay measuring cAMP accumulation. The 5HT7A receptor isoform is the most predominant isoform expressed in human brain (limbic brain regions that regulate motions, mood and cognition) over 7B and 7D. Since aripiprazole was not tested in these assays, no comparison is possible.
Brexpiprazole showed to be a moderate partial agonist towards the 5HT2C (VSV) receptor using the [35S]-GTPγS assay. The 5HT2C (VSV) receptor isoform was selected for functional assay since it is one of the predominant splice variant isoforms expressed in human brain. Despite being 2-fold potent and 2-fold affine to 5HT2C (VSV) than aripiprazole, brexpiprazole showed similar Emax vs serotonin (approx 10%).The Applicant did not perform any functional assay for human D4 and 5HT1B receptors for which brexpiprazole showed a moderate binding affinity (Ki = 6.3 and 32 nM, respectively).

Adrenergic receptors

Brexpiprazole showed high affinity towards the human adrenergic receptor alpha 1B (Ki = 0.17 nM), alpha 2C (Ki = 0.59-1.0 nM), and alpha 1D (Ki = 2.6 nM), moderate affinity to the alpha 2A receptor (Ki = 15-21 nM), alpha 2B receptor (Ki = 17 nM), beta 1 receptor (Ki = 59 nM) and beta 2 receptor (Ki = 67 nM), low binding affinity to the beta 3 receptor (47% inhibition at 10 µM).
A complete cellular functional screening of brexpiprazole on adrenergic receptors was performed. Brexpiprazole showed potent antagonism on alpha 1B (cIC50 = 0.66 nM cAMP accumulation assay) and alpha 1A receptors (cIC50 = 5.0 nM calcium mobilization assay), moderate antagonism at alpha 1D (cIC50 = 19 nM inositol-1-phosphate) and alpha 2C receptors (cIC50 = 62 nM cAMP accumulation

assay), and low antagonism at beta 1 (cIC50 = 160 nM cAMP accumulation assay), alpha 2A (cIC50 >140 nM impedance assay), alpha 2B receptor (cIC50 >1200 nM cAMP accumulation assay), beta 2 receptor (cIC50 =230 nM cAMP accumulation assay), and beta 3 receptors (no significant inhibition at 10 µM, cAMP accumulation assay). Since aripiprazole was not tested in these assays, no direct comparison is possible; it is known that qualitatively aripiprazole shares the same adrenergic profile with brexpiprazole. However, brexpiprazole showed a 60-100 fold difference in affinity vs potency (antagonism) at the human alpha 2C receptor unlike aripiprazole and the reason for this difference, remains unclear.

Histaminergic receptor

Brexpiprazole showed a moderate binding affinity to H1 receptor (Ki 19 nM) on which acted as a moderate antagonism (cIC50 = 6.8 nM).

In summary, in *in vitro* human cloned receptors, brexpiprazole showed a high binding affinity for $5HT_{1A}$ > alpha1B > D2L > 5HT2A > alpha2C. Its intrinsinc activity as partial agonist is: 5HT1A > D2L > D3. Its antagonistic potency is: alpha1B > alpha1A > 5HT2A.While affinity and potency were overall higher compared with aripiprazole, Emax values were overall lower than aripiprazole. In conclusion, the lower intrinsic activity at D2 receptors makes brexpiprazole a step closer to D2 antagonism on the agonist-antagonist spectrum. Along with less intrinsic ability to D2 receptor, brexpiprazole has a greater potency than aripiprazole with regard to D2, D3, 5HT1A alpha1A receptors.

Brexpiprazole **major human metabolite DM-3411** displayed affinity for several human receptors although in a lower extent than the parent compound. High affinities (Ki ≤5 nM) were observed for 5HT2A, 5HT2B, and D2L receptors, while moderate affinities (Ki between 5 and 100 nM) were shown for D2Short > 5HT1A > D3 > α1B > H1 > α1A > 5HT7. At D2L receptor the binding affinity of DM-3411 was approx 10-fold lower than the parent compound. Regarding its functionality, DM-3411 was a weaker partial agonist (Emax 22%) on 5HT1A vs brexpiprazole. It acted as an antagonist towards 5HT2B receptor showing 63% inhibition in IP1 assay. Differently from brexpiprazole at D2Short and D3 receptors DM-3411 acted as antagonists with potencies of 4.1 nM and 38 nM, respectively. The quite potent antagonism of metabolite DM-3411 towards dopaminergic receptors is not in line with the partial agonism of brexpiprazole. It should noted that D2Short receptors are mainly autoreceptor (differently from the primarily a postsynaptic D2L isoform receptor) which provides feedback inhibition that controls cell firing and the synthesis, release, and uptake of dopamine; antagonism at D2S receptors increases dopaminergic release.
Although in PK distribution study, DM-3411 was not detected in the rat brain following single oral dose of 1000 mg/kg dual-label 14C-brexpiprazole (report 020074), no brain distribution studies was carried out in monkey and/or human tissues. Although with 16-fold lower affinity than brexpiprazole, DM-3411 still binds with high affinity to hD2L receptor (Ki =5 nM) and it showed a potent antagonism activity to hD2Short (IC50<5 nM). A weaker than to D2L antagonist activity was also observed to hD3 receptors. Differently from brexpiprazole, DM-3411 had no effect (agonist or antagonist) for 5HT2A receptors although it bound highly to them. DM-3411 bound to rat 5HT1D moderately (Ki 48 nM) showing an intrinsic activity (Emax) of 55% (impedance assay).
DM-3411 showed a much lower ability than brexpiprazole in binding the human dopamine transporter (50% vs 90%) and similar ability to bind serotonin tranporter (approx 65%). However, DM-3411 will unlikely influence the central effects of brexpiprazole in humans due to its poor CNS permeability demonstrated in rat following oral administration and its unability to increase dopamine release in microdialysis study in the rat.

Other minor metabolites of brexpiprazole were detected to be able to bind to human D2 receptors. These are OPC-54050 (0.518 nM), DM-3404HCL (0.324 nM), DM-3412 (0.175 nM), DM-3413 (0.355 nM), each with very similar Ki value to the parent compound (0.295 nM), and are therefore considered to be pharmacologically active. However, according to results from multiple dose mass balance clinical trial (CSR 331-08-205), the potential patient exposure to metabolites of brexpiprazole - DM-3411, DM-3412, OPC-54050, DM-3404HCL, DM-3413 and SFO-34318, is negligible sufficiently low enough to have no or limited pharmacological contribution to the overall pharmacological effect. A single metabolite was detected at low levels in the rat brain, SFO-34318, however it is acknowledged that this metabolite has limited capacity for pharmacological activity due to its low affinity for human D2 receptors.

In vivo occupancy, mechanistic, and behavioral studies were also performed.In 2 separate studies *in vivo* receptor binding and ex vivo autoradiography in rat brain, a time-dependent brexpiprazole binding was observed with 90% maximal occupancy at 5HT1A, 75% to 80% maximum occupancy to D2, and more moderate occupancy (maximal at 56 and 41%) at both 5HT7 receptors and SERT. Brexpiprazole occupancy profile mirrored the *in vitro* rat binding affinity except for 5HT2A receptor for which the *in vivo* (cortex) occupancy was higher than the *in vitro* binding affinity data in rat cloned receptor (Ki= 3.8 nM).
Brexpiprazole plasma (trunk blood, 2 hrs post dose) exposure was strongly correlated to receptor occupancies differently from aripiprazole: in rats, about 50% of D2 and 5HT2A receptors were occupied at plasma concentrations reached with oral doses lower than 5 mg/kg (i.e. 49 ng/ml reached with 2.5 mg/kg; 91 ng/ml reached with 4.6 mg/kg). Indeed, in classical behavioural experiments for D2 antagonist antipsychotics (see later on), the ED50 for brexpiprazole was lower or close to 5 mg/kg value. However, *in vivo* receptor occupancy cannot be considered without taking into account intrinsic activity at D2 receptors and other determinants for the clinical outcome of the medicinal product: receptor state (e.g. high/low affinity), density and sensitivity, activation of presynaptic or reserve receptors, basal level of dopamine, modulatory effect by concomitant activation of different receptors (e.g. brexpiprazole partial agonism to 5-HT1A receptor which regulate dopaminergic neuronal activity).

These rat plasma concentrations/receptor occupancy curves were used by the Applicant to extrapolate human information. In the 2.6.2.6.1 section of the "Pharmacology Written Summary", the Applicant stated the following: ", Figure 2.6.2.6.1-1 was generated to illustrate a simulation of estimated receptor binding occupancy of several 5-HT receptors in human generated by combining results from *in vivo*/ex vivo binding studies in rats and D2 receptor occupancy study in human patients using positron emission tomography (PET). *[from Phase I single oral dose of OPC-34712, Protocol 331-07-202]"*. This strongly suggests that at the maximum recommended human dose (MRHD) (ie, 4 mg), a substantial level of binding would be expected on these receptors in patients."

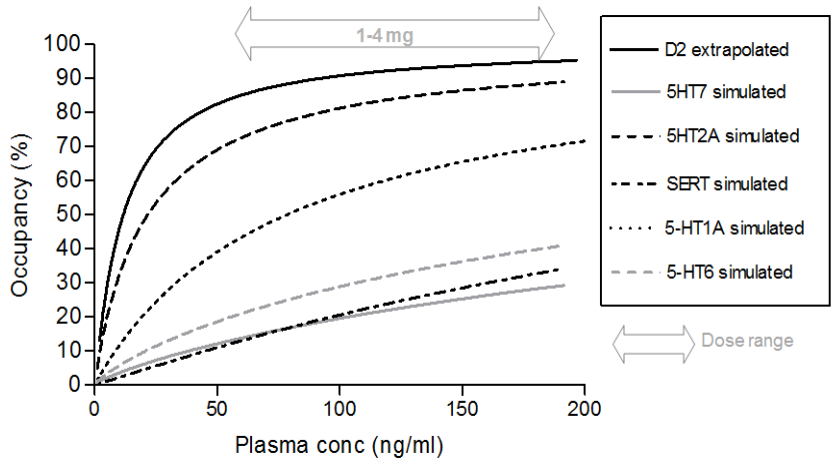


Figure 2.6.2.6.1-1 Human Occupancy Simulations for Brexpiprazole
Human occupancy simulations for brexpiprazole at the D2 receptor are from human PET data. The estimated human occupancy levels at other targets were calculated from results of rat *in vivo* and ex vivo binding studies and the PET study.101 The estimated occupancy ranges at different steady-state human doses/exposures are indicated by boxes.

The Applicant's conclusions regarding the PD (receptor occupancy)/PK (plasma concentrations from rat trunk blood) correlation, extrapolated by rat data, that "this strongly suggests that at the maximum recommended human dose of 4 mg, a substantial level of binding would be expected on these receptors *[D2, 5HT2A, 5HT1A]* in patients." appears not adequately supported by clinical evidence for which no clear dose-response relationship can be obtained. From the figure above, it seems that even at plasma strengths lower than those obtained in patients administered with 4 mg/day, a high receptor occupancy predictive of clinical outcome, is reached. The therapeutic window of most antipsychotics in adults with schizophrenia is generally recognized as 60–80% occupancy of striatal D2 receptors; greater receptor occupancy can lead to cognitive dysfunction as reviewed by *Gerretsena et al., 2017 and Reeves et al., 2017*.
A number of rat microdialysis studies were performed in order to investigate the effect of brexpiprazole on extracellular levels of neurotransmitters in brain.
Acute OPC-34712 > 10 mg/kg slightly inhibited basal levels of extracellular dopamine and moderately increased its metabolites 3,4-dihydrox-phenylacetic acid (DOPAC) and homovanillic acid (HVA) in the nucleus accumbens microdialysate collected 3-hrs post orally dosed rats. This effect correlated with brexpiprazole relative intrinsic activity at dopamine hD2L receptors and was intermediate to that produced by dopamine D2 receptor partial agonists with higher relative intrinsic activity (e.g. (-)3-PPP, and aripiprazole) and to that of the dopamine D2 receptor antagonist olanzapine. This is consistent with *in vitro* biochemical evidence that brexpiprazole is a dopamine hD2L receptor partial agonist with a lower relative intrinsic activity than aripiprazole. The fact that brexpiprazole (and aripiprazole) did not stimulate large increases in extracellular dopamine, DOPAC and HVA can be due to their partial agonism to 5-HT1A receptor which regulate dopaminergic neuronal activity.

Dose-dependent increase of DOPAC and HVA levels was also observed in microdialysate samples of medial prefrontal cortex collected 3-hrs post dose of freely-moving orally dosed rats. These effects were qualitatively similar to those produced in the same brain region after acute aripiprazole treatment.

No effect on basal extracellular dopamine, norepinephrine and serotonin was recorded in medial prefrontal cortex and ventral hippocampus in microdyalisates collected up to 180 min post-dose, and in medial prefrontal cortex of freely-moving orally administered rats no extracellular acetylcholine levels were induced by brexpiprazole while a dose-dependent histamine extracellular levels increase was

observed in microdyalisates collected up to 200 min post-dose: this latter may be likely mediated by histamine H1 antagonism (hH1 cIC50=6.8 nM) (report 14805).

Local infusions of brexpiprazole into the ventral hippocampus and the medial prefrontal cortex of freely moving rats saw dose-dependently increased extracellular levels of serotonin but exerted no effects on DA and NA levels. This suggests that the lack of effect after systemic administration could be due to the multi-receptor profile of brexpiprazole, in which its effect in one brain region may mask the effect in other brain regions. Since in the same study, a local infusion of the selective α2 adrenoceptor antagonist idazoxan enhanced hippocampal serotonin levels, the Applicant's hypothesis that brexpiprazole ability to increase serotonin levels could be mediated by its antagonism to α2-adrenoceptors is plausible even if no functional study was performed on rat adrenergic receptors. Overall, OPC-34712 and aripiprazole have the potential to regulate prefrontocortical dopamine function due to their additional action as serotonin 5-HT2A receptor antagonist and serotonin 5-HT1A receptor partial agonist.

Effects on some functional CNS effects mediated by pre- and postsynaptic D2 receptors and by 5HT2A receptors were explored *in vivo* in rats.

In electrophysiological studies in chloralhydrate-anaesthetized rats dosed IV with brexpiprazole and in some cases with aripiprazole, in presynaptic areas (autoreceptors) brexpiprazole acted as a potent 5-HT2A antagonist, a 5-HT1A agonist, and a D2 partial agonist. Compared to aripiprazole, brexpiprazole is a more potent 5-HT1A agonist with less intrinsic activity at D2 autoreceptor. In postsynaptic areas, brexpiprazole acted as an antagonist on α1B- and α2-adrenoceptors, the latter located on 5-HT terminals. Systemic administration of brexpiprazole did not alter the action of the 5-HT and NE transporters, and does not change the responsiveness of 5-HT1A and α2-adrenoceptors found on pyramidal neurons in the CA3 region of hippocampus. Furthermore, local application of brexpiprazole showed full agonistic action on postsynaptic 5-HT1A receptors.

In rats treated with SC reserpine and IP 3-hydroxybenzyl-hydrazine dihydrochloride (NSD-1015), a DOPA decarboxylase inhibitor, oral administration of brexpiprazole (1 hour before the sacrifice) significantly inhibited the reserpine-induced increase in DOPA accumulation in rat striatum but in a lower manner than aripiprazole (2 hour before the sacrifice). These results suggest that brexpiprazole has a slightly lower presynaptic dopamine autoreceptor agonistic activity than aripiprazole.

Dopamine released by the hypothalamus acts as a hormone to inhibit release of prolactin via activation of D2 receptors in anterior pituitary cells. Brexpiprazole was able to significantly decrease serum hyperprolactinemia induced by reserpine only at low dose of 3 mg/kg in male rats 1 hour before sacrifice. In contrast, the D2 receptor antagonist risperidone further increased prolactin levels in male rats pretreated with reserpine. The difference between these compounds can be associated with the partial agonist activity of brexpiprazole on D2 receptors of the anterior pituitary cells. However, it should be noted that in toxicity study 020467, brexpiprazole increased the serum prolactin levels in both male and female rats following a single oral administration at 100 mg/kg for males and 30 mg/kg for females about 7- and 99-fold than the control after 1 hour after administration. Notwithstanding its partial agonism, the ability to increase serum prolactin levels was also observed in clinical trials. In the Phase II short-term controlled trial the incidence of prolactin elevations observed in the brexipiprazole 2-4 mg group (13.7%) and in the 4 mg/day group (15.3%) was higher than the one observed with both aripiprazole (0) and quetiapine (8.2%), even though the limited number of patients included in the active comparator groups should be taken into account in the interpretation of data (see Clinical safety

section). The lower intrinsinc activity as D2 agonist respect aripiprazole, which makes brexpiprazole a step closer to D2 antagonism, could be responsible to this effect.

Brexpiprazole was assessed in a series of behavioural studies in rats and monkeys predictive of antipsychotic activity. Oral administration of brexpiprazole significantly inhibited the serotonin 5-HT2A/2C receptor agonist (±)-2,5-dimethoxy-4-iodoamphetamine (DOI)-induced head twitch in rats in a dose dependent manner. The effect of brexpiprazole (administered 1 hour before before the injection of DOI) was weaker than those of olanzapine and risperidone and stronger than that of aripiprazole (administered 2 hours before the injection of DOI). These results suggest that OPC-34712 has a postsynaptic serotonin 5-HT2A receptor antagonistic action *in vivo* stronger than aripiprazole.

The atypical antipsychotics olanzapine and risperidone have been shown to have lower incidence of the extrapyramidal symptoms (EPS) and sedative side effects in clinic than the typical antipsychotic haloperidol. Catalepsy and ptosis responses are considered as animal models reflecting the EPS and sedation. Brexpiprazole induced catalepsy with the maximum response observed at 6 hours postdose: in terms of both EC50 and onset time, this effect was stronger than that of aripiprazole and milder than that of atypical antipsychotic risperidone. The same trend was observed for ability to induce ptosis.

Inhibition of conditioned avoidance response (CAR) in rats trained to avoid foot shock after a warning tone, is considered as one of the most predictive tests to evaluate the effects on positive symptoms of schizophrenia. The dose-dependent effect of oral brexpiprazole in inhibit the conditioned avoidance response in rats was stronger than that of aripiprazole and was almost comparable to those of atypical antipsychotics olanzapine and risperidone. It is noted that brexpiprazole and the other compounds were administered 1 hour before the observation while aripiprazole was given 2 hour before testing. However, these results account for a lower intrinsic activity of brexpiprazole to D2receptors.

The effects on apomorphine (APO)-induced behaviours (hyperactivity and stereotypy in rats and eye blinking in monkeys) are classical tests for D2 antagonist antipsychotics. APO-induced hyperlocomotion was inhibited in rats in a dose-dependent manner following a single oral dose of brexpiprazole. This effect was milder than haloperidol and stronger than that of aripiprazole both of which also significantly inhibited this behavior. It should be noted that while aripiprazole was administered 2 hour before SC injection of APO, the other compounds were administered 1 hour prior APO injection. However, these results account for a lower intrinsic activity of brexpiprazole to D2 receptors.

The effect of brexpiprazole on APO-induced stereotyped behavior was evaluated in rats. Single oral doses of brexpiprazole significantly inhibited stereotyped behavior in a dose-dependent manner. The effect of brexpiprazole was more potent than that of aripiprazole, weaker than those of haloperidol and almost comparable with that of olanzapine and risperidone. These results suggest that OPC-34712 has a postsynaptic D2receptor antagonistic action *in vivo*, comparable to current available antipsychotics tested. Aripiprazole was orally administered to rats 2 hours before the SC injection of APO while all other compounds were orally administered to rats 1 hour before APO injection.

Combining results from the 4 studies in rats (on EPS, on conditioned avoidance response, on APO-induced hyperlocomotion and stereotyped behavior), the catalepsy and ptosis liability values were calculated by the Applicant respect the EPS. The conclusions that OPC-34712 has more possible risk to cause a sedation than both aripiprazole and haloperidol (study report 020417) and to induce less sedative effect than olanzapine and risperidone in (study report 020244) and that OPC-34712 has a lower propensity to induce EPS than those of the atypical antipsychotics (olanzapine and risperidone)

and the typical antipsychotic (haloperidol) (study report 020417), are not easily traslated into clinical setting since clinical trials used different comparator. Anyway, it is noted that in short term controlled trials 2-4 mg brexpiprazole showed an higher rate of sedation than placebo and EPS-related TEAEs (mainly driven by akathisia events) higher than placebo was observed only for 4 mg. Both akathisia and sedation are reported as common adverse drug reactions in SmPC section 4.8 and akathisia as an important identified risk in RMP is also supported by non-clinical data.

Spontaneous eye blinking is thought to reflect central dopaminergic function and frequent eye blinking occurs in schizophrenia. Single oral doses of brexpiprazole were able to inhibit APO-induced eye blinking in a dose-dependent manner in monkeys. This result indicates that brexpiprazole has a D2 receptor antagonistic action in cynomolgus monkeys.

It is known that chronic treatment with D2 receptor antagonist's increases sensitivity of postsynaptic receptors in animals and humans, possibly by increasing the maximum number of binding sites (Bmax) in the well-known phenomenon of up-regulation. The hypersensitivity of the D2 receptor induced by chronic administration of antipsychotics is considered a possible cause of tardive dyskinesia. Repeated oral doses of brexpiprazole (6 mg/kg) equivalent to haloperidol 1 mg/kg/day for 3 weeks in rats did not relevantly enhanced APO-induced stereotyped behavior in rats (borderline p value 0.0489 vs haloperidol). These results indicate that the repeated administration of OPC-34712 has at least a comparable potential to enhance sensitivity of postsynaptic D2 receptors than haloperidol; whether this translates in a similar potential to induce the tardive dyskinesia haloperidol should be assessed in clinical chronic setting.

Cognitive impairments are a common feature of several psychiatric disorders, such as schizophrenia. Disturbed cognitive function is observed across a number of domains, including episodic/working memory and executive function. Recently, novel rat models have been suggested to mimic cognitive deficits in schizophrenia, *e.g.*, deficits after withdrawal of subchronic treatment with the noncompetitive NMDA receptor antagonist, phencyclidine (PCP). Different cognitive functions were used for the characterization of brexpiprazole action in comparison to aripiprazole.

Acute administration of brexpiprazole dose-dependently reduced the discrimination index (i.e. time spent exploring the novel object adjusted for total exploration time) in subchronic Phencyclidine (subPCP)-treated rats in a discrete assay/model system, namely the novel object recognition (NOR) validated by Lundbeck. In contrast, aripiprzole failed to attenuate the subPCP-induced deficits in novel object exploration.
In a follow-up study it was shown that both 5-HT1A receptor partial agonism and 5-HT2A receptor antagonism contributes to the procognitive activity of oral brexpiprazole (3 mg/kg).The Applicant concludes that results are suggestive of brexpiprazole procognitive activity in declarative memory, object recognition memory, long-term memory even if no explanation was given for the different behavior shown by aripiprazole although the 5-HT1A partial agonism and 5-HT2A receptor antagonism are shared.

Secondary pharmacodynamic studies

Brexpiprazole was tested for additional activity across a wide spectrum of receptors, ion channels and transporters in an *in vitro* study at a concentration of 10 µM. The inhibition ratios of Brexpiprazole were 52.23% to 100.00% for α2-adrenergic (non-selective), β-adrenergic (non-selective), dopamine transporter (human), muscarinic (non-selective), muscarinic M1 (human), Na channel site 2,

neurokinin NK1 (human), neurokinin NK2 (human), opiate (non-selective), opiate μ (human), oxytocin, serotonin transporter (human), sigma (non-selective), and monoamine oxidase (MAO-B).

Both aripiprazole and brexpiprazole showed a pattern of effects consistent with an antiimpulsivity therapeutic effect in a behavioral paradigm of impulsivity using the Five Choice Serial Reaction Time Test (5CSRTT) in rats. The effects were seen at the lower oral doses in the following range used aripiprazole at 3.0 and 10.0 mg/kg and brexpiprazole at 0.1, 0.3, and 1.0 mg/kg, with higher doses resulting in a reduction in responding. Attention and impulsivity are characteristics of several disease states including mild cognitive impairment, schizophrenia and ADHD.

Using a recent rat model for post-traumatic stress disorder (PTSD)-related memory typical feature in the anxiety disorder, oral administration of brexpiprazole 0.03-0.3 mg/kg, administered 7 days after the fear conditioning, reverses the paradoxical pattern of PTSD-like memory, restoring thereby a normal contextual fear memory.

Safety pharmacology programme

In a battery of safety pharmacology studies, brexpiprazole was evaluated for effects on central nervous system (CNS), respiratory system, and cardiovascular system. Brexpiprazole induced dose dependent CNS depression and decrease in body temperature at 30 and 100 mg/kg doses, corresponding to an AUC_{0-24} (derived by toxicokinetic data at day 1 in the 4 week rat study 019254) of 3601 and 19928 ng.h/mL. The NOAEL for CNS effects is 10 mg/kg (AUC_{0-24} 1754 ng.h/mL). Exposure margins (5.0) in excess of the human AUC of 3950 ng.h/mL at the maximum human recommended dose (MHRD) of 4 mg exists only for the higher dose used, therefore brexpiprazole-induced CNS depression effect is likely relevant, consistently with what is observed in clinical (depression (8 of 2869 subjects 0.3%) was the most frequently occurring serious TEAE in Trial 331-10-238).

No effect on the respiratory system of rats was seen, when administered up to 30 mg/kg.

Concerning cardiovascular system there was an effect on human *ether-à-go-go*-related gene (hERG) tail current by brexpiprazole with an IC50 of 0.12 μM, i.e. concentration hundreds of times higher than the one reached in patients treated with the brexpirazole MHRD (corresponding to approximately 4 ng/mL of free brexpiprazole, due to its 98% binding to plasma proteins). *In vivo* brexpiprazole administered orally at 30 mg/kg (Cmax 2048, exposure margin 10) in conscious adult dogs (report 019648) induced a prolongation of the QT interval and QTc. Moreover, prolonged QT and QTc were also observed in monkeys at 10 (Cmax 496.9 ng/mL, exposure margin 2.5) and 30 mg/kg/day (Cmax 1427 ng/mL, exposure margin 7.2) on Day 1 in the 4- and 13-week repeated dose studies respectively, and in the juvenile dog toxicity report at 30 mg/kg, corresponding to brexpiprazole exposure in excess of about 10 fold of the clinical exposure at the MHRD.
The Applicant considers that QT effect may be indirectly associated with the brexpiprazole pharmacologically-mediated decrease in body temperature, but no findings of dog lower body temperature were recorded by the Study Director of the report 019648. Even though the *in vitro* and *in vivo* effects are observed at much higher concentration and exposure (approximately 2.4-7.1 fold in term of Cmax at which QT prolongation is most closely associated) than those reached in patients treated with brexpiprazole MHRD, the effects on QT prolongation associated with brexpiprazole administration may be considered to represent a potential risk to patients particularly at dose initiation,

even in light of available clinical data (Clinical Trial 331-10-242) in which significant signs of QT prolongation have been observed in female patients (see Clinical efficacy section).
No hERG study data has been provided for DM-3411. The relative exposure of DM-3411 has been indicated to be 162 ng/ml (Cmax) and 3320 h.ng/ml (AUCt) from the clinical thorough QT study. In addition, exposure at the maximum daily dose would result in plasma levels of the parent and metabolite well below levels expected to cause an arrhythmogenic effect.

Brexpiprazole at oral doses >3 mg/kg induced hypotension. The Applicant provided sufficient data supporting the hypothesis of decreased blood pressure in dog by blockade of α1-adrenoceptors in peripheral blood vessels, as observed with risperidone. This is adequately reflected in SmPC section 5.3.

Pharmacodynamic drug interactions

The current RXULTI application is for approval of brexpiprazole as monotherapy in the treatment of schizophrenia. Anyway, concomitant medications are commonly used in schizophrenic patients: e.g. antidepressants, anxiolytics. Since pharmacology of brexpiprazole is believed to be mediated by a combination of activities at multiple monoaminergic receptors, the potential for pharmacodynamic drug-drug interactions is to be considered. In the absence of non-clinical and clinical pharmacodynamic drug interaction studies, adequate information on the most commonly concomitant medications sharing the same brexpiprazole targets or adverse effects is reflected in the RXULTI SmPC section 4.5.

2.3.3. Pharmacokinetics

The PK of brexpiprazole was investigated in a number of *in vitro* and *in vivo* studies conducted in mice (*in vitro* only), rats, rabbits, dogs, and monkeys, including studies of brain concentration for brexpiprazole and its metabolites. The PK of the major metabolite DM-3411 (the S-oxide of the benzothiophene moiety of brexpiprazole), was also assessed.

Analytical methods using HPLC with UV detection and LC-ESI-MS/MS were validated to quantify concentrations of unlabeled brexpiprazole or the metabolites DM-3411 and other metabolites and reference compounds in plasma (mouse, rat, rabbit, dog, and monkey), in mouse skin homogenate, in matrices obtained from *in vitro* protein binding (ie, mouse, rat, monkey, and human serum and dialysate) and from rat hepatic S9 sample mixtures. The LLOQ for brexpiprazole was 1 ng/mL in rat, dog, and rabbit plasma, and 0.3 ng/mL in monkey plasma.

Absorption
In fed conditions, absorption was dose dependent in male rats and cynomolgus.
AUC in fed female rats orally administered with 3 mg/kg were 1.50 fold higher than those in the male fed rats and feeding (assessed only in male rats) reduced absorption. The absolute bioavailability of bexpiprazole in male rat at 1 mg/kg was only 13.6%. In fed conditions in dogs, Cmax and AUC∞ were approximately 3.0 to 3.7 times of the values obtained under the fasted conditions. Thus, feeding increased the plasma concentration profiles of OPC-34712 after a single oral administration of 30 mg/kg to the male beagle dogs. In fed conditions, AUC in male fasted cynolgus orally administered with 3 mg/kg were higher (1.3 times) than those in the male fed cynomolgus. The absolute bioavailability of bexpiprazole in male cynomolgus at 1 mg/kg was only 31%.
Following oral administration, an approximately linear PK profile was observed in rats and monkeys species used in toxicological evaluations. In both rat and monkey a food effect reducing absorption of brexpiprazole was observed (differently from the dog). In fed female rats a higher exposure was

observed compared to the male fed rat. In contrast to human bioavailability (95%), brexpiprazole showed low bioavailability in rats (13.6%) and monkeys (31%).

Distribution
In vitro, brexpiprazole was highly bound to serum protein in all tested species (Mouse, Rat, Rabbit, Dog, Monkey, Human). Brexpiprazole was bound predominantly to albumin and α1-acid glycoprotein in human serum. At brexpiprazole concentration saturating the binding sites (higher than the clinical Cmax of 199 ng/ml (clinical tral 331-08-205), digitoxin was able to displace brexpiprazole (6.6-9.1%) to serum protein binding; howevr, this extent is not considered clinically relevant. Neither warfarin nor diazepam affected brexpiprazole binding to human albumin.

In vitro, DM-3411 protein binding in the the monkey and human sera was lower than that of brexpiprazole.

In vivo brexpiprazole protein binding in rat and monkey plasma was lower than *in vitro* protein binding, ranging from 91.8% and 94.0% in rat and 93.9% and 95.5% in monkeys; no gender effect in rat and no overall time dependency was observed up to 48 hours. From clinical studies, brexpiprazole bound human plasma protein to 99%.

Following oral administration in rats, the concentration of radioactivity in all tissues in female rats (except for sex organs) was like that of male rats with radioactivity peak in all tissues 0.5 to 8 hours postdose. Concentrations in the CNS were generally lower than in plasma and were quantifiable up to 24 hr post-dose in males and up to 8 hr post-dose in females. The radioactive concentrations in plasma and brain of brexpiprazole and metabolite DM-3411 were higher for collectively housed rats compared with individually housed rats. The Applicant attributed this difference in the mean values could be a function of the variability introduced by the small number of animals (N = 5) in each group. An uneven brexpiprazole distribution pattern was observed: almost no radioactivity was observed in the white matter.

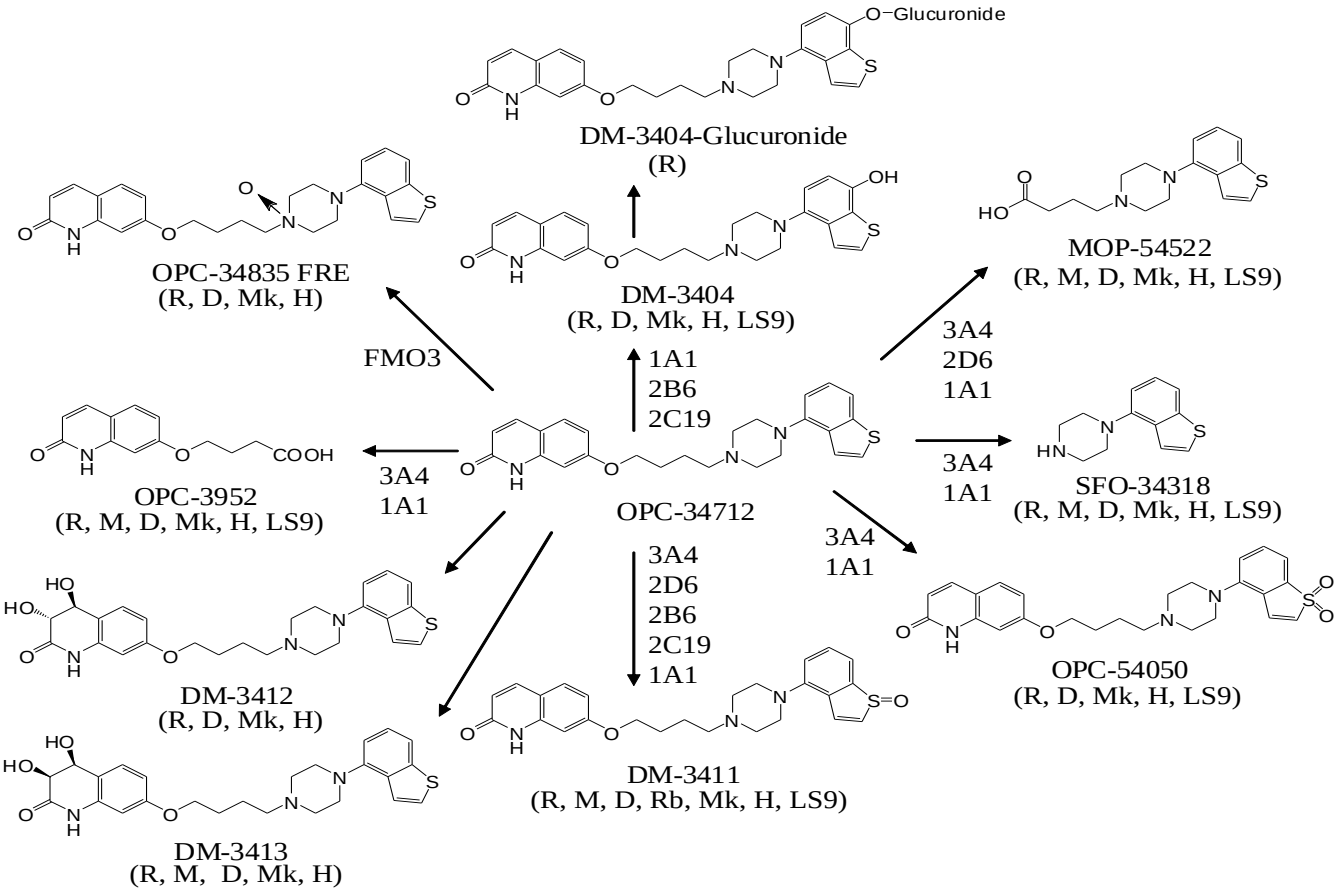
The major metabolite DM-3411 was not detected in rat CNS; since no brain distribution study was performed in other species nor in human. It is not possible to exclude a different behaviour of DM-3411 in CNS.

In autoradiograpy study, brexpiprazole and/or its metabolites tend to be distributed in the gray matter containing the neuronal cells not but the white matter containing the myelinated fiber and oligodendrocytes. From these results, there was no evidence on the relationship between the cerebral distribution of this drug and the brain lesions (demyelination and necrosis of the oligodendrocytes in the neurotoxicity toxicity studies 019906 and 20278).

Results from pregnant rats indicate that brexpiprazole and its metabolites are transferred into the fetus at concentrations that were generally comparable to levels seen in maternal blood. Brexpiprazole and its metabolites are excreted into rat breast milk.
In pigmented rats (Long-Evans) orally administered with a single dose of 3 mg/kg, concentration of radioactivity in the skin was higher than those in plasma and non-pigmented skin: although these results suggest brexpiprazole has an affinity for melanin, brexpiprazole resulted non-phototoxic in *in vivo* studies in albino and pigmented mice (see Toxicological section).
Brexpiprazole displays evidence of binding to melanin, with retention to the skin and eyes in several animal species. In addition, in brexpiprazole was photocytotoxic to cultured mammalian cells

(BALB/3T3 cells) *in vitro*. There is no evidence of potential phototoxicity related to this enhanced retentionanyway brexpiprazole is anticipated to be used chronically with the potential of dose accumulation to melanin containing tissues. Given the absence of toxicological findings the retention to skin and eyes may have limited clinical implications.

The proposed **metabolic** pathways of brexpiprazole (OPC-34712) in animals and humans is depicted below:



M = mouse, R = rat, D = dog, Rb = rabbit, Mk = monkey, H = human, LS9 = liver 9000 × g supernatant (S9) fraction. Source: Reports: 019018, 019521, 019635, 020277, 023749, 023880, 024026, 024102, 024787, 331-07-201, 331-08-205 and 331-08-206.

Metabolic fate of brexpiprazole was investigated with *in vitro* and *in vivo* studies.
In rat liver S9 fraction, the S-oxide of the benzothiophene structure of brexpiprazole (DM-3411) resulted the most abundant brexpiprazole metabolite across species (mouse, male rat, rabbit, dog, monkey, human) except in the famale rat. In human, brexpiprazole was mainly metabolized to DM-3411 by CYP2D6 and CYP3A4. This was also demonstrated by the fact that in human liver microsomes ketoconazole (a known CYP3A4 inhibitor) inhibited the formation of DM-3411 approx. 70%.

Brexpiprazole showed a high inhibitory potential to CYP2B6 isoform (Ki=5.01 μM) in human liver microsomes and a small induction potential to CYP1A2, CYP3A4/5 and CYP3A4 activity in primary cultured human hepatocytes.

In conclusion, the biotransformation profiles of brexpiprazole were qualitatively similar across species. CYP3A4 was the primary enzyme responsible for metabolism of brexpiprazole in human liver microsomes.

DM-3411 did not significantly inhibit several CYP isoenzyme while no induction potential by DM-3411 was assessed.

In vivo
In dedicated *in vivo* studies in rat and monkey, DM-3411 was confirmed to be the major metabolites across species contributing to 23.6% of the overall administered dose. Based on overall exposure, DM-3411 was the most abundant metabolite in plasma from male and female rats with no marked sex differences were observed. Being pharmacologically active in rat, monkey and human, DM-3411 was fully characterized from the safety point of view (see Toxicological part of this AR). Safety margins of DM-3411 based on exposure at NOAELs are consistently below 1, except for male rats in the fertility study (3.6-fold), and female rats in the embryo-fetal development (1.7-fold) and carcinogenicity (1.6-fold) studies.

Excretion
Excretion studies were conducted in rats and monkeys, evaluating the extent of elimination following single oral administration of radiolabelled ^{14}C-brexpiprazole. In both female and male rats and male monkeys unchanged brexpiprazole was eliminated mainly with feces and excretion was almost complete by 168 hr post-dose: in rats >93% of recovered radioactivity was present 168 hours post-dose; in monkeys, recovery was lower than in rats at 63% with a greater extent present in urine (15%). In male and female bile duct-cannulated rats, more than 71% of radioactivity was present in urine and bile.

Pharmacokinetic drug interactions
Brexpiprazole was not an MDR1 substrate but it together with DM-3411 inhibited the digoxin transport meditated by MDR1. Brexpiprazole was not a substrate of BCRP transporter but it together with DM-3411 inhibited BCRP efflux transporter. However, Results of DDI trials have further confirmed that the administration of brexpiprazole had no effect on the MDR1 (Pgp) (fexofenadine used as substrate) or BCRP transporters (rosuvastatin used as substrate). Both Brexpiprazole and DM-3411 slightly inhibited BSEP.
Brexpiprazole is not a substrate of OATP1B1, OATP1B3 or OCT1 transporters. Brexpiprazole and DM-3411 inhibited OATP1B1, OCT2, and OCT1. Brexpiprazole showed no inhibition of OAT1 and OAT3-mediated transport and DM-3411 has weak inhibitory potency for OAT1 and OAT3-mediated transport. Brexpiprazole and DM-3411 showed no inhibition of OATP1B3-mediated transport. Brexpiprazole and DM-3411 had an inhibitory potency against the MATE1- and MATE2-K.
Overall, based on the results from *in vitro* CYP, transporter studies, and clinical DDI studies, the potential for brexpiprazole or DM-3411 to produce systemic drug-drug interactions appears minimal.

2.3.4. Toxicology

Rats and cynomolgus monkeys were used in general dose-repeat toxicity studies. They are considered relevant species for assessment of human safety due to presence of the pharmacological target, and comparable metabolic profile with humans, although the very low exposure reached in monkeys is acknowledged.

Single dose toxicity

Acute toxicity of brexpiprazole was tested in rats and monkeys by oral and i.v. administration up to 2000 mg/kg. The Approximate Lethal Dose in male and female rats was >2000 and >800 mg/kg respectively by the oral route and >1.2 mg/kg by i.v. route. In monkeys, the ALD was >100 mg/kg by oral route and > 0.56 mg/kg by i.v. route.

Behavioural signs observed in these studies were consisted of CNS effects (hypoactivity, closed eyes, and abnormal postures) and hypothermia.

In 13-week (pre-carcinogenicity) repeated dose toxicity in **mice** orally administered, no target organs was identified, decrease in body weight with a remarkable decrease in food consumption, incomplete eyelid closure, staggering gait and creeping, were observed. These changes did not differ from those observed in rats and monkeys.

Repeat dose toxicity

Repeated dose oral toxicity evaluations in **rat** included studies of 1 and4-week (non-pivotal) and 13 (+4-week recovery), and 26 (+13-week recovery) week duration. In the 1-week study doses were 300 and 1000 mg/kg/day, in the 4-week study, doses were 30, 100, and 300 mg/kg/day, in the 13-week study the doses were 30, 100, 300 (M)/10, 30, 100 (F) mg/kg/day, and in the 26-week study the doses were 3, 10, 30 and 100 mg/kg/day. In all studies, there was a largely consistent pattern of observations including decreases in body weight gain and food consumption, incomplete eyelid closure, hypoactivity, lacrimation, creeping, staggering gait, poor physical condition (consistent with the depression of CNS as the brexpiprazole pharmacodynamic effects), hyperreactivity and aggressiveness that might be excessive adaptive-responses to the brexpiprazole-induced depression of CNS.

Flaccidity and dilatation of the scrotum in male rats during 26-week study have been attributed by the Applicant to brexpiprazole activity on dopaminergic receptors as the same effects were reported in the rats 12-month repeated oral dose toxicity study of perospirone, another atypical antipsychotic (*Yamada T. "Twelve-month repeated oral toxicity report of SM-9018 in rats." CLINICAL REPORT - Basic and Clinical Report*).

Although the causes of male reproductive organs alterations were not definitively discussed, the effect on scrotum seems not to be clinically relevant, since it was not observed in monkeys nor in humans and no impairment of male reproductive function were detected.

Clonic convulsions occurred at exposure in term of AUC_{0-24} of about 11 fold higher than that reached in patients receiving the MHRD of 4 mg/kg of brexpiprazole. Clonic convulsion seems to depend more on the duration of treatment than on the amount of exposure. In fact, this effect has not been observed in rats treated for 13 weeks at a dose of 100 mg/kg/d corresponding to exposure about 15 times higher than that reaches at the MHRD. In clinical long-term controlled Trial 331-10-232, there were no reports of TEAEs associated with seizure in any treatment group during the Double-blind Maintenance phase of Trial, but during the Stabilization Phase, convulsion was reported in 1 subject, who was treated with brexpiprazole 4 mg/day: the event resolved and the subject continued the trial. Therefore, clonic convulsion although no longer present during the recovery phase of the report, is judged to be a toxic change in rats due to brexpiprazole exposure. Clonic convulsion/seizure is regarded as a dopamine underactivity condition mediated by dopamine antagonist agents (Starr, 1996). "Seizure" is considered a potential risk for humans in the RXULTI RMP and adequate warning in SmPC section 4.4 is included for patients who have a history of seizure disorders or have conditions associated with seizure.

Haematology and clinical chemistry changes induced by brexpiprazole are considered not toxicologically relevant due to their sporadic nature, the absence of a doseresponse relationship, small magnitude of change, almost total reversibility, and possible association with decreased food consumption and body weight or stress and absence in monkeys and in humans.

Brain lesions were observed in rats at brexpiprazole exposures about 29 and 7 fold higher for males and females respectively, than the exposure in patients receiving the MHRD. The lesion included necrosis of oligodendrocytes, demyelination, and vacuolation of white matter or gray matter, chromatolysis of neurons; necrosis of granule cells in olfactory bulb; and necrosis of Purkinje cells. The incidence of these lesions was low and these lesions were observed primarily in rats which had severe hypothermia, died or were moribund (i.e., a time-dependent change could not be demonstrated). Besides findings in the rats, chromatolysis of neurons was also observed in non-human primates; however the finding was only noted in the moribund animals and was considered secondary to poor food consumption, deteriorating condition and once again low body temperature. The Applicant hypothesis that brain lesions (necrosis of oligodendrocytes, demyelination, and vacuolation of white matter or gray matter, chromatolysis of neurons; necrosis of granule cells in olfactory bulb; necrosis of Purkinje cells) observed in rat and monkey are related to hypothermia is shared. Indeed, when alleviation of hypothermia was reached through group housing (5 rats per polycarbonate cage with paper pulp bedding) prevention of brain lesions were observed. Finally, the cause of histopathologic lesions in the brain was considered to be pharmacologically-induced hypothermia, rather than a direct toxic effect of brexpiprazole.
Thermogenesis is under direct control of the CNS, and an effect on thermogenesis (such as hypothermia) has been observed with other centrally-acting drugs. In the SmPC it is reported the disruption of the body's ability to reduce core body temperature. In the All Phase (1/2/3) Brexpiprazole Trials Safety Sample one TEAE of hypothermia (1/7897, 0.01%) occurred. This adverse event of hypothermia occurred in a, enrolled in Trial 331-13-214, evaluating brexpiprazole as an adjunctive therapy in MDD. The subject was on brexpiprazole 2 mg plus venlafaxine. The non serious adverse event of hypothermia occurred 21 days after the last brexpiprazole dose. The outcome of the event was reported as not recovered. Review of the vital signs during the trial did not provide any abnormality for body temperature (baseline 36.2°C; lowest value at Week 14: 35.9°C on 17 Mar 2016). The investigator assessed the event as mild and not related to the investigational medicinal product. Thus, the non-clinical observation of brain lesions in rat and monkey attributed by the Applicant to hypothermia apparently does not find a correlation in clinical experience up to now. Anyway, temperature regulation disorder (e.g. hypothermia, pyrexia) is reported in the table of ADRs (frequency not known) in RXULTI section 4.4 SmPC risk of hyperthermia, is indicated in the SmPC section 4.4 under "Neuroleptic Malignant Syndrome (NMS)" and "Body temperature regulation" headings.
In conclusion, since available data do not allow to rule out a possible association between hypothermia and brexpiprazole administration, hypothermia should be monitored in upcoming PSURs.

Spermatogenesis, hypertrophy of corpus luteum, uterus atrophy and mucification, increased ovary weights and increased incidence of lobular hyperplasia with secretion of milk in the mammary gland (pseudopregnancy) and femminization of mammary gland in males observed at high doses, are considered consequences of drug-related pharmacologically mediated hyperprolactinemia.

In the 13 week rat study focal myocardial necrosis was observed in controls (4), 3 mg/kg/day (4), 10 mg/kg/day (4), 100 mg/kg/day (8) and the 300 mg/kg/day (6) groups. After a 4 week recovery period focal myocardial necrosis was seen in the control (1) and at 300 mg/kg/day (2), and focal myocardial fibrosis, an anatomic repair-finding to myocardial necrosis, in the control (1) and at 300 mg/kg/day (4). According to the literature this finding is commonly found as a spontaneous lesion in the rat with limited implications for humans. There does not appear to be a dose-related event and there is increased incidence in the brexpiprazole treated animals, although it is agreed that this is not to a great extent.

The toxicological meaning of deposition of pigment granules observed in many organs of male and female rats at exposures in term of AUC_{0-24} 3-fold higher that corresponding to the MRHD, could not be definitively clarified, but the relevance of this finding to humans is not certain.

Most changes observed during the dosing phase of 13- and 26-week studies in rats resolved during the 4 week recovery periods, except the pigment granules deposition for the adrenal, thyroid, and ovary ah the highest doses.

Repeat dose oral toxicity evaluations in **monkey** included studies of 2- and 4-week (non pivotal) and 13 (+4 week recovery), 39-week duration. In the 2-week supplementary study performed to calculate the NOEL value, the doses were 0.03 and 0.1 mg/kg/day, in the 4-week study the doses were 3, 10, and 30 mg/kg/day, in the 13- and 39-week studies the doses were 1, 3 and 30 mg/kg/day, while. Similar to studies in the rat, there was a largely consistent pattern of observations linked to brexipirazole pharmacodynamics. Unlike the rat, tremors, limited to the extremities in 4- and 13-week studies and whole body tremors in the 39-week studies, were observed. The Applicant considered tremors of extremities not toxicologically significant since similar signs were also observed during the pre-test phase ECG in 9/16 animals/sex, and whole body tremors an adaptive response to cold due to reduction of body temperature consistent with the pharmacology of brexpiprazole. However, this explanation does not originate by the conclusion of Study Director of the 39-week study, in which the observed whole body tremors was not explained and the tremors observed at the low dose were judged incidental. Tremors are not considered mediated by pharmacological CNS depression. The whole tremors are present at exposures even lower than those observed in patient receiving the therapeutic dose of brexpiprazole, and they are not reversible in females monkeys dosed at exposure 1.3 fold higher that reached in patients. Tremors are one of the signs of tardive diskinesia associated with long-term use of antidopaminergic agents characterised by irreversibility after removal of the antidopaminergic agent (*Ure et al., 2016*). This is likely mediated by sensitisation of D2 recepotors. In pharmacodynamic study 020354, repeated administration of 6 mg/kg brexpiprazole showed at least a comparable potential to enhance sensitivity of postsynaptic D2 receptors than haloperidol. Whole body tremors observed in 39-week toxicity study in monkeys are considered as an acute pharmacological effect rather than a late effect due to prolonged D2 blockade such as tardive dyskinesia. The partial agonist feature of brexpiprazole makes its safety profile different from that of antipsychotic agents known to cause tardive dyskinesia. However, the lower intrinsic activity of brexpiprazole at D2 receptors than aripiprazole (relative to dopamine -Emax, %- 40% vs 60%) makes brexpiprazole a step closer to D2 antagonism on the agonist-antagonist spectrum.
Atrophy of the thymus, adrenals and spleen observed at high doses were considered to be associated with a stress response. The etiology of hyperemia of the oral mucosa was not further discussed by the Applicant, but the presence only in 13-week report at 2.5 x exposure margins in term of clinical exposure and the full recovery, allows to consider this finding of uncertain nature and not clinically relevant.

In 39 weeks study at Day 273 TK values at 30 mg/kg/day were lower than those observed on Day 1 or Day 91, and the decline was as much 60% lower, e.g., in females. The Applicant cannot confirm on the basis of TK/NOAEL obtained in repeated-dose toxicity studies, that the monkey is the non-rodent relevant animal species for toxicity extrapolation to human. The absence of margins of exposure, especially in monkey is due to the fact that brexpiprazole toxicity observed in mice, rats and monkeys was mainly related to its exaggerated pharmacological activity (e.g. hypoactivity, hypothermia or hyperprolactinemia). The lower exposure seen in female monkeys at 30 mg/kg/day on Day 273 in

39-weeks monkey study, was justified due to high variability in the measured plasma concentrations coming from only 2 animals.

Genotoxicity

The **genotoxic** potential of brexpiprazole was investigated in a bacterial reverse mutagenicity assay, an *in vitro* mammalian mutagenicity assay in L5178Y tk+/- Mouse Lymphoma cells and two *in vivo* rat bone marrow micronucleus tests with a two day exposure period and in unscheduled DNA Synthesis Test. The Applicant conclusion is that brexpiprazole was weakly genotoxic at cytotoxic doses in the *in vitro* mammalian cell reports, however since brexpiprazole was negative in the bacterial reverse mutation test and in the *in vivo* genotoxicity tests (bone marrow micronucleus, *in vivo/in vitro* unscheduled DNA synthesis) no mutagenic potentials emerged. It is therefore considered that the available evidence from genotoxicity investigations are affected by some uncertainties. With regard to the Unscheduled DNA Synthesis, in fact it is considered a test with scarcely sensitivity. With regard to the micronucleus *in vivo* test on bone marrow, the Applicant clarified that the highest doses used in the *in vivo* micronucleus test (2000 mg/kg and 1000 mg/kg in male and female rat, respectively) were selected on the basis of previous toxicity studies i.e. single dose toxicity study 018982 and the non-pivotal repeated dose toxicity study 019075, in which unfortunately no TK analysis was performed. Athough no toxicity sign at the bone marrow has been descripted in the *in vivo* micronucleus test, the highest doses used in this genotoxicity study were much higher than doses used in pivotal repeated toxicity studies in rat (e.g. 300 mg/kg in male, and 100 mg/kg in female) for which systemic exposure was reached. Since the bone marrow is a well perfused tissue it is asssumed that brexpiprazole exposure to the bone marrow was reached.

Carcinogenicity

The **carcinogenic** potential of brexpiprazole was studied in CD-1 mice at doses of 0.75, 2 or 5 mg/kg/day and in SD rats at doses of 1, 3, or 10 mg/kg/day in males and 3, 10 or 30 in females. In mice at the highest dose, systemic exposure attained a 3.1x and 1.1x multiple of human therapeutic exposure in male and female mice, respectively in term of AUC. In rats exposure multiples of 1.0x and 4.4x were achieved in the high dose males and females, respectively in term of AUC. At the maximum dose, in male and female mice, exposure at steady state was approximately 3.1x and 1.1x, respectively, the human exposure associated with 4 mg brexipriprazole (3950 ng.h/mL). Although the proposed safety margin for mice and rat carcinogenicity is quite low, both assays are considered overall adequate. In both cases the doses were recommended by the FDA CDER's Executive Carcinogenicity Assessment Committee. In mice the 0.75, 2, and 5 mg/kg doses used are based on mortality in both sexes and the excessive decrease in body weight in males at doses >10 mg/kg observed in the 13-week subchronic toxicity reports and the exposure to parent brexpiprazole and its main metabolite during the report period was confirmed in TK groups. In rats the MTD was achieved as decreased body weight gain associated with decreased food consumption was observed in high dose groups (the final body weigh was lower by 19% in high dose -males and by -13% at medium dose and -28% in high dose females). Survival was unaffected by brexpiprazole treatment.
In CD 1 mice daily oral gavage administration of brexpiprazole to male up to 91 weeks and to female up to 98 weeks at dosages of 0.75, 2 and 5 mg/kg/day, revealed no notable changes in tumorigenic potency in males, but revealed degenerative changes in mammary glands and pituitary in females given >0.75 mg/kg/day without dose related difference. The Applicant's current hypothesis of the pathophysiologic mode of female mammary gland and pituitary carcinogenesis is that brexpiprazole induces a cascade of non-genotoxic events initiated by brexpiprazole dopamine "D2 antagonistic effect" that block dopaminergic receptors promoting prolactin secretion. This hypothesis is mainly based on results of two additional studies showing that brexpiprazole has a potency to increase the serum

prolactin levels in male and female rats with a single oral administration of the compound at 100 mg/kg for the males and 30 mg/kg for the females, and in the female and male mice with at 5 mg/kg, with potency judged to be weaker in the males when compared to that of the females in both species. The more remarkable serum prolactin levels of the females than those of the males are reflected in the results of the CD-1 mice carcinogenicity assay. Antipsychotic agents are demonstrated to promote the secretion of prolactin from the pituitary gland by their blocking action on the dopaminergic receptors in mice (*Xu et al., 2002*), supporting the Applicant argumentation that brexpiprazole had a potency to increase the serum prolactin levels through dopamine "D2 antagonist effect" in mice. It should be of note that increased mortality associated with the occurrence and incidence of mammary tumour and pituitary gland tumour only in mice and not in rats was also reported for another "D2 partial agonist" ["In mice, dietary administration of aripiprazole at doses of 1, 3, and 10 mg/kg/day for 104 weeks was associated with increased incidences of mammary tumours, namely adenocarcinomas /adenoacanthomas and pituitary adenomas in females at the mid- and high doses. Increases in mammary and pituitary neoplasms as well as other drug-related mammary/reproductive tissue alterations in females were considered, by the applicant, likely to be secondary to aripiprazole-related increases in serum prolactin" Abilify EPAR EMA].

On these bases the hyperprolactinemia hypothesis for mice female tumours is considered plausible taking also into account that no pattern of change was observed for other hormones linked to mammary tumours. Hyperprolactinaemia is **not** rodent-specific: prolactin related effects are seen across studies and in all species.
Regarding the *in vitro* findings for brexpiprazole and its metabolite, DM-3411, and D2 antagonistic activity, the applicant confirms that these antagonistic effects may contribute to findings of hyperprolactinaemia. Hyperprolactinaemia and related disorders, has been raised as an important potential risk in the Risk Management Plan (RMP).

The role of prolactin in human breast tumours remains unsettled. Several studies have linked hyperprolactinemia to an increased risk of breast cancer (*Halbreicht et al., 2003; Hankinson et al., 1999*). Several epidemiological studies have investigated whether female psychiatric patients receiving antipsychotics have a higher incidence of breast cancer, with conflicting results. However, the study performed with the most strong methodology (retrospective cohort design and comparison between women who were exposed to antipsychotics with age-matched women) found that antipsychotic dopamine receptor antagonist conferred a small but significant risk of breast cancer (*Wang et al., 2002*). Conversely, other studies (*Cohen et al., 2000; Mandalà et al., 2002*) have shown no correlation between hyperprolactinemia and breast cancer. Therefore, at this time we have no definitive data suggesting increased risk of breast cancer secondary to hyperpolactinemia caused by antipsychotics, and further prospective studies with large number of patients are considered desirable in this area before a definitive answer can be provided (*Vyas, 2012*). The same author recommends detection of existing mammary tumours before examination or studies (mammogram) prior administration of neuroleptics. In light of current knowledge, the induction of mammary neoplastic lesions by hyperprolactinemia cannot yet be considered definitively an exclusive 'rodent-specific' phenomenon as stated by the sponsor Available clinical data derived only by short-term trials, showed that median prolactin values increased from baseline in the brexpiprazole 2 to 4 mg/day group and were more pronounced in females compared with males and in general the increase in prolactin was not associated with an adverse clinical outcome (i.e., AEs potentially related to prolactin elevation).
The NOAEL for mice tumorigenicity was not determined for female i.e. no margin exists for female, and considered 5 mg/kg/day for male mice at this dose level the AUC_{0-24} is 12430 ng.h/mL, corresponding to a margin of exposure of 3.1.

In SD rats no brexpiprazole related neoplastic lesions were observed up to 10 mg/kg/day (M) and 30 mg/kg/day (F) administered for 104 weeks.
Regarding non neoplastic lesions, yellowish brown pigments in cortical cells and macrophages in the adrenals were observed in the 26-week repeated oral dose toxicity report and these pigments were considered to lipofuscin. Although the deposition of yellowish brown pigment in cortical cells and macrophages is a spontaneous change observed in aged rats, the mechanism of pigment deposition was unclear. In lungs, white focus represented alveolar foamy cells in histopathological examination and severe changes were observed only in the high dose group. Similar changes were reported in the 26-week repeated oral dose toxicity study but the causes of these changes were not clarified. Atrophy of the pituitary pars intermedia observed also the 26-repeated oral dose toxicity report was considered to be pharmacologically mediated and secondary to the D2 partial agonistic activity of brexpiprazole as a D2 agonist, bromocriptine, reduced the number of cell layers of the pituitary pars intermedia (supporting publication provided). Also, the finding has little or no relevance to humans since humans have no distinct pars intermedia.

Retinal changes observed in carcinogenicty rat assay were considered by the Applicant "to be a spontaneous change observed in aged rats and there were no clear differences in the incidence or severity of retinal atrophy among the animals that were sacrificed as scheduled, it is considered to be related to the increase in survival rate in females and not related to administration of the test article". Bilateral retinal degeneration was also observed in rat carcinogenicity reports with aripiprazole attributed to the greater lifetime exposure to light due to a higher survival rate in these groups. On these bases retina effects is not considered related to the pharmacological profile of brexpiprazole or aripiprazole. Although statistically significant, non-neoplastic and retinal changes observed in carcinogenicity rat assay were considered to be of limited toxicological significance. The Applicant presented historical data on retinal atrophy up to 2012 of the test facility Gotemba Laboratory in which brexpiprazole rat carcinogenicity study was performed. The incidences of retinal atrophy observed with brexpiprazole were within the range of the incidence of spontaneous lesions observed in the historical control database and the apparent increase in the incidence of retinal atrophy in the brexpiprazole treated groups reflects the increased survival of animals in the treated groups, especially females, and is not of toxicological significance.
The NOEL for tumorigenicity in the rat was determined to be 10 and 30 mg/kg/day for male and female respectively; at this dose level the AUC $_{0\text{-}24}$ is 3912 ng.h/mL for male and 17409 ng.h/mL for female, corresponding to a margin of exposure of 1.0 and 4.4, respectively.

Reproduction Toxicity

In the **rat fertility and early embryonic developmental toxicity** study, male fertility was unaffected up to 100 mg/kg, but male fertility end-point effects/test effects were noted in the general toxicology studies and dog juvenile toxicology study. Prolonged estrus and decreased fertility (pregnancy rate of 80.0% and 78.9%, respectively, as compared with 95.0% in controls) at 3 and 30 mg/kg (4.1 exposure margins in term of AUC) were observed in female rats, as well as increased pre-implantation losses at 30 mg/kg (17.7% vs 3.0% in control 3.0%). These findings are likely to be related to the increase serum prolactin induced by brexpiprazole.
The NOAEL for female rat reproduction was 0.3 mg/kg/day (, 0.3 exposure margins in terms of AUC).
In the **preliminary rat embryo-foetal developmental toxicity** study, the high dose, 100 mg/kg/day, was clearly shown to be (above) the Maximum Tolerated Dose (MTD), since only 1 litter remained for investigation due to maternal mortality in 3 dams and complete litter loss in 3 dams. Two related skeletal malformations were observed at this high dose level; namely cervical vertebrae, absence of vertebral arch and deformed vertebral arch were seen in one fetus (R7) in one litter (F10027)

with no observations in controls or other dose groups. Since the incidence is low and seen at a dose level at or above the MTD, the findings should be interpreted with caution. One visceral malformation (ventricular septum defect in one fetus) was also observed at 30 mg/kg/day with no observations in the control group.
In the **pivotal rat embryo-foetal developmental toxicity** study, ventricular septum defect was observed in 2 control fetuses (from 2 litters) and in 1 fetus at the highest dose tested 30 mg/kg/day. Based on the incidence of the findings in the control group, the observation is considered likely incidental. The fact that litters only from the control and only the high dose group (30 mg/kg/day), is consistent with ICH S5. Moreover, data from the pilot study show that at lower doses (10 mg/kg) no obvious signs of teratogenic effects. The lack of TK data in pregnant rats is considered a weakness in the evaluation especially since pregnant rats seem more sensitive to brexpiprazole toxicity than non-pregnant females as the NOAEL for general toxicity in female rats was 10 mg/kg/day (hypoactivity and closed eye) in the 13- and 26-week repeat dose studies, while being 3 mg/kg/day in the pivotal embryo-foetal development study.
Anyway, limited differences in distribution of radiolabelled brexpiprazole in pregnant and non-pregnant rats was observed, being the only difference distribution to the submaxillary gland in pregnant animals, which may not be of toxicological significance.
Data from the preliminary and pivotal studies suggest a steep dose-toxicity response relationship, as about a doubling of the estimated exposure at a well-tolerated dose, resulted in high maternal toxicity. Overall, it is agreed that no clear signs of fetal malformations were observed in brexpiprazole-treated animals when tested up to the approximate clinical AUC exposure (estimation based on TK data in non-pregnant rats).
The NOAEL for rat general toxicity in dams is considered 3 mg/kg/day, for reproductive effects in dams and embryo-foetal development is considered to be 30 mg/kg/day.

In the **preliminary rabbit embryo-fetal developmental toxicity** study there appeared to be a decrease in implants at 100 and 150 mg/kg, an increase in preimplantation and slight decrease in live foetuses (although not statistically significant) at both these doses. At 150 mg/kg/day microphthalmia in one fetus and narrowed aortic arch in two fetus were observed. This was not seen in control. Thymic remnant was seen in the neck in 3 animals at 150 mg/kg and in 1 control. Eigth lumbar vertebrae were seen in 7 controls and 16 animals at 150 mg/kg/day. Fused sternebrae was seen at 3 at 150 mg/kg/day: these findings were not seen in controls.
In the **pivotal rabbit embryo-fetal developmental toxicity study** no effect on foetal viability was observed at any dose (10, 30, or 150 mg/kg/day). Foetus malformations were seen only at the highest dose 150 mg/kg (~16-fold the clinical AUC): vertebral malformations were noted in 3 fetuses from 2 litters. These skeletal malformations although seen at a low incidence were not observed in the control group and their incidences are outside the historical control data of the test facility and of that reported in the literature. In addition, the incidence of the visceral malformation (absence of gall bladder) seen in 2 foetuses of 1 litter is also outside the historical control data and literature data.
The NOAEL for rabbit general toxicity in dams is considered 10 mg/kg/day, for reproductive effects in dams and embryo-foetal development is considered to be 30 mg/kg/day.

In **rat pre- and postnatal toxicity study** brexpiprazole caused neonatal toxicity (delayed growth and physical development and impaired viability) at a dose level inducing maternal toxicity (3 mg/kg/day), including impaired nursing behaviour. Foetus and milk transfer of [14C]-brexpiprazole after administration to rats was demonstrated.

The RMP was satisfactorily updated as regards the non-clinical safety findings on reproductive/developmental toxicity and their relevance to the use in humans.

Other toxicity studies

Brexpiprazole does not pose risk for irritancy and haemolytic potential.
Brexpiprazole did not exert any effects on the sheep red blood cells -specific antibody response in rats under up to 30 mg/kg /day administered once daily for 4 weeks. Moreover, weight of evidence demonstrates that brexpiprazole is not immunotoxic in the species used in the preclinical studies and therefore is not considered to have an immunotoxic potential in humans under the conditions of therapeutic use.
The calculations provided by the Applicant for class 2 Drug Substance impurity is agreed and the proposed specification provides safety margins in excess of unity. It has been identified that impurity is non-genotoxic following the conduct of QSAR analysis (DEREK NEXUS and Leadscope methods). The impurity is present at levels below ICH Q3A levels for qualification.

The specified impurities were tested for genotoxic properties in bacterial reverse mutation assay providing negative results ..

The negative result in the two appropriate *in vivo* phototoxicity report supersedes the positive *in vitro* result. Therefore, brexpiprazole was not considered to be phototoxic.

As regard the abuse liability/potential, brexpiprazole was considered to possess discriminative stimulus effects in rats but no withdrawal signs suggestive of physical dependence production were evident in rats, nor reinforcing effect in the i.v. self-administration experiment in rhesus monkeys. No withdrawal signs were recorded in the recovery periods of the rat and monkey repeated dose toxicity studies.

2.3.5. Ecotoxicity/environmental risk assessment

Summary of main study resultsSubstance (INN/Invented Name): brexpiprazole			
CAS-number (if available): 913611-97-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential log K_{ow}	OECD TG 123	**2.41, 4.27, 4.86** at pH 5, 7, 9 respectively	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	bioconcentration factor (BCF)	10875 L/kg fresh weight (fw)	Very B (enzyme induction)
Persistence	DT50 or ready biodegradability	DT50 $_{\text{whole systems, 12 °C}}$:>10.000 d Plateau formation in water/sediment system. (Not readily biodegradable)	Very
Toxicity	NOEC	72-h NOEC=EC10 alga 0.011 mg/L	Not T
PBT-statement :	**Brexpiprazole is very persistent and very bioaccumulative (vPvB) but**		

	not toxic substance.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	**0.02**	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OPPTS TG 830.1110	Koc = 20249 to 24780 L/kg			One sludge, different ratios (mean values) Terrestrial base set studies required
Ready Biodegradability Test	OECD TG 301	Not biodegradable			Water/sediment study (OECD TG 308) triggered
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 $_{whole\ systems,\ 12\ °C}$:>10.000 d Plateau formation in water/sediment system. Only marginal CO2 formation (3.1 %). % shifting to sediment > 10 at Day 14 and any point in time thereafter			Very persistent in the aquatic environment. . Sediment organism effect study required
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	No observed effect concentration (NOEC) = EC10	ca. 11	µg/L	Pseudokirchneriella subcapitata, geometric mean of initially measured value and ½ LOQ, degradation ca. 90% assumed to be photodegradation
Daphnia sp. Reproduction Test	OECD 211	NOEC = EC10	130	µg/L	Nominal concentration
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210 flow-through	NOEC	56	µg/L	Danio rerio, arithmetic mean measured value, nominal 40 µg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	> 770 µg/L (ie, the limit of water solubility)	µg/L	No Observed Effect Loading Rate (NOELR) ≥ 100 mg/L
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	10875	L/kg	%lipids: 5, low dose

			and 6662	fw	% lipids: 5, high dose
Aerobic and anaerobic transformation in soil	OECD 307	DT50 12°C, geomean %CO2	140 d 4.7 %		P
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	≥ 1000	mg/ kg	Soil dry weight
Terrestrial Plants, Growth Test/Species: • Onion (Allium cepa, Alliaceae, Monocotyledonae) • Maize (Zea mays, Poaceae, Monocotyledonae) • Beetroot (Beta vulgaris, Chenopodiaceae, Dicotyledonae) • Tomato (Lycopersicon esculentum, Solanaceae, Dicotyledonae)	OECD 208	NOEC	≥ 1000	mg/ kg	Soil dry weight
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	≥ 1000	mg/ kg	Soil dry weight
Collembola, Reproduction Test	ISO 11267	NOEC	250 mg/kg	mg/ kg	Soil dry weight EC10 = 152 mg/kg
Sediment dwelling organism	OECD TG 218	NOEC	1000	mg/ kg	Sediment dry weight, Chironomus riparius

Brexpiprazole is very persistent and very bioaccumulative, but not toxic substance: possible enrichment of brexpiprazole in terrestrial food chains might pose a concern; this is reflected in section 5.3 and 6.6 of the SmPC.
Post-approval, the PECsediment and PECsoil will be calculated using the adsorption data (Koc) in soil from the OECD 106 study and the SimpleTreat model described in the European Union System for the Evaluation of Substances (EUSES). Revised risk assessments will be provided for the sediment dwelling organism study and the terrestrial effects studies. An updated ERA report will then be submitted with the revised risk assessments.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed: The Applicant should perform an OECD 106 study to determine the adsorption of brexpiprazole in three soils and the re-evaluate the ERA once completed.

2.3.6. Discussion on non-clinical aspects

Brexpiprazole (OPC-34712, OPC-331, and Lu AF41156) is intended to treat schizophrenia in adult patients. Dopamine overactivity is traditionally considered as the main cause in the occurrence of psychotic disorders and it can be pre-synaptic (an excess of dopamine release from dopaminergic nerve terminals) or postsynaptic (an increase in the density of D2 receptors or an increase in post-receptor action).

The pharmacological *in vitro* and *in vivo* profile of brexpiprazole is mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors and is qualitatively very similar to aripiprazole (Abilify, indicated for the treatment of schizophrenia and from the same MAH of Rxulti): their common denominator is their partial antagonism at 5HT2A and D2 receptors with high 5HT2A/D2 affinity ratios (both for human 1.6 and rat 1.1 receptors). They can activate D2 receptors, but they can also dampen the action of the endogenous transmitter dopamine on D2 receptors; this dampening of dopamine is directly proportional their intrinsic activity.

Brexpiprazole showed a high binding affinity (Ki) for human cloned receptors: 5HT1A (0.12-0.15 nM) > alpha1B (0.17 nM) > D2L (0.3 nM) > 5HT2A (0.47 nM) > alpha2C (0.59-1.0 nM), D3 (1.1 Nm) and showed antagonistic potency (IC50) towards: alpha1B (0.66 nM) > alpha1A (5.0 nM) > 5HT2A (6.5 nM).

In terms of intrinsic activity, brexpiprazole showed a lower Emax than aripiprazole to D2L (40 vs 60 nM) and D3 (15 vs 28 nM) receptors and, in a lesser extent, to 5HT1A (60 vs 73 nM).

The lower intrinsic activity at D2/D3 receptors makes brexpiprazole a step closer to D2 antagonism on the agonist-antagonist spectrum.

Brexpiprazole showed a moderate binding affinity to H1 receptor on which acted as a moderate antagonism.

Along with less intrinsic activity to D2, D3 and 5HT1A receptors, affinity (Ki) and potency (ED50) were overall higher compared with aripiprazole; this accounts for *in vivo* lower effective doses respect to aripiprazole.

It should be noted that for the functional characterization, the GTPγS binding assay is the most reliable functional test for G protein coupled receptors (GPCRs) since it reflects events close to the receptor and so results are not subject to strong amplification unlike other more downstream assays for GPCRs, for example, inhibition of cAMP which results may be higher as compared with corresponding values in GTPγS binding assays (Payne et al., 2002). Unfortunately, this endpoint was only used in brexpiprazole functional assays on 5HT receptors thus no sound comparison could be done across brexpiprazole functionality on the different receptors tested.

Brexpiprazole was able to inhibit human dopamine (90%) and serotonin (65%) efflux transporters.

Brexpiprazole major human metabolite DM-3411 displayed affinity for several human receptors although in a lower extent than the parent compound. Regarding its functionality, DM-3411 was a weaker partial agonist (Emax 22%) on 5HT1A vs brexpiprazole and differently from brexpiprazole at D2 Short and D3 receptors. DM-3411 acted as antagonists with potencies of 4.1 nM and 38 nM, respectively. It should be noted that antagonism at D2S (mainly auto-receptors) increases dopaminergic release. The contribution of DM-3411 to the clinical outcome of brexpiprazole as full dopaminergic antagonist cannot be excluded.

Differently from brexpiprazole, DM-3411 had no effect (agonist or antagonist) for 5HT2A receptor although it bound highly to it. DM-3411 showed a much lower ability than brexpiprazole in inhibit the human dopamine transporter (50% vs 90%) and similar ability to bind serotonin transporter (approx 65%).

Other minor metabolites (OPC-54050, DM-3404HCL, DM-3412, DM-3413) had a great affinity to human D2 receptors with Ki < 0.6 nM.

In rat brain the brexpiprazole receptor occupancy profile mirrored the *in vitro* rat binding affinity except for 5HT2A receptor for which the *in vivo* (cortex) occupancy was higher than the *in vitro* binding affinity. Following oral administration a time-dependent brexpiprazole binding was observed with 90% maximal occupancy at 5HT1A, 75% to 80% maximum occupancy to D2, and more moderate occupancy (maximal at 56 and 41%) at both 5HT7 receptors and SERT. Exposure was strongly correlated to receptor occupancies differently from aripiprazole: about 50% of D2 and 5HT2A receptors were occupied at plasma concentrations reached with oral doses lower than 5 mg/kg (5 mg/kg is the brexpiprazole EC50 for classical behavioural experiments for D2 antagonist antipsychotics).

Results from microdialysis in orally administered rats showed no effect on basal extracellular norepinephrine and serotonin. The moderate increase in extracellular dopamine and its metabolites 3,4-dihydrox-phenylacetic acid (DOPAC) and homovanillic acid (HVA) was between the increase produced by aripiprazole and the full D2 antagonist olanzapine. This confirms the *in vitro* brexpiprazole D2 partial agonism. The dose-dependent extracellular histamine level increase observed may be likely mediated by brexpiprazole histamine H1 antagonism.

Electrophysiological studies in rats dosed IV with brexpiprazole and in some cases or aripiprazole, further confirmed the *in vitro* brexpiprazole multimodal activity on D2 and 5HT receptors: at D2 presynaptic areas (auto-receptors) brexpiprazole showed a slightly lower agonistic activity than aripiprazole.
In addition, the postsynaptic 5HT2A antagonistic action *in vivo* was confirmed with the ability of brexpiprazole to inhibit the 5HT2A/2C receptor agonist (±)-2,5-dimethoxy-4-iodoamphetamine (DOI)-induced head twitch.

In male rats brexpiprazole was able to significantly decrease serum hyperprolactinemia induced by reserpine only at low oral dose of 3 mg/kg: with brexpiprazole at 10 and 30 mg/kg no difference from reserpine hyperprolactinemia control value was observed. On the contrary, all doses of the D2 receptor antagonist risperidone further increased prolactin levels. It should be noted that in toxicity study brexpiprazole increased the serum prolactin levels in both male and female rats following a single oral administration at 100 mg/kg for males and 30 mg/kg for females about 7- and 99-fold than the control after 1 hour after administration. Notwithstanding its partial agonism, the ability to increase serum prolactin levels was also observed in clinical trials. The lower intrinsinc activity as D2 agonist respect aripiprazole, which makes brexpiprazole a step closer to D2 antagonism, could be responsible to this effect.

In a series of behavioural studies in rats, single oral administrations of brexpiprazole was able to:
- induce catalepsy and, to a less extent, ptosis responses (which are considered as animal models reflecting the extrapyramidal symptoms and sedation) only at high doses;
- inhibit the conditioned avoidance response;
- inhibit the apomorphine (APO)-induced hyperlocomotion;
- inhibit APO-induced stereotyped behavior.

In all the above mentioned studies the effect of brexpiprazole mediated by postsynaptic D2 receptor antagonism was stronger than aripiprazole, weaker than haloperidol and almost comparable to atypical antipsychotics, olanzapine and risperidone. These results account for a lower intrinsic activity of brexpiprazole to D2receptors.
In short term controlled trials 2-4 mg brexpiprazole showed a higher rate of sedation than placebo and extrapyramidal symptoms (EPS)-related TEAEs (mainly driven by akathisia events) higher than placebo

were observed only for 4 mg. Both akathisia and sedation are reported as common adverse drug reactions in SmPC section 4.8 and EPS is listed as important identified risk in the RMP and it is the only one also supported by non-clinical data.

Single oral doses of brexpiprazole were able to inhibit APO-induced eye blinking in monkeys. This result indicates that brexpiprazole has a D2 receptor antagonistic action in cynomolgus monkeys.

Repeated administration (3 week) in rats of oral doses of brexpiprazole equivalent to haloperidol showed at least a comparable potential to enhance sensitivity of postsynaptic D2 receptors than haloperidol measured as enhanced APO-induced stereotyped behavior. The hypersensitivity of the D2 receptor induced by chronic administration of antipsychotics is considered a possible cause of tardive dyskinesia.

No off targets activity of brexpiprazole was observed in a binding assay towards several receptors, channels and enzymes. The potential to be helpful in cognitive impairment in psychotic disorders was shown.

In rats brexpiprazole induced dose dependent CNS depression and decrease in body temperature at 30 and 100 mg/kg doses at exposure margins (5.0) in excess of the human AUC of 3950 ng.h/mL at the maximum human recommended dose (MHRD) of 4 mg only for the higher dose used; therefore, brexpiprazole-induced CNS depression effect is likely relevant, consistently with what is observed in clinical.

No effect on the respiratory system of rats was seen, when administered up to 30 mg/kg.

Concerning cardiovascular system brexpiprazole administered orally at 30 mg/kg (Cmax 2048, exposure margin 10) in conscious adult dogs induced a prolongation of the QT interval and QTc. Moreover, prolonged QT and QTc were also observed in monkeys at 10 (Cmax 496.9 ng/mL, exposure margin 2.5) and 30 mg/kg/day (Cmax 1427 ng/mL, exposure margin 7.2) on Day 1 in the 4- and 13-week repeated dose studies respectively, and in the juvenile dog toxicity report at 30 mg/kg, corresponding to brexpiprazole exposure in excess of about 10 fold of the clinical exposure at the MHRD. Even though the *in vitro* and *in vivo* effects are observed at much higher concentration and exposure than those reached in patients treated with brexpiprazole MHRD, the effects on QT prolongation associated with brexpiprazole administration may be considered to represent a potential risk to patients particularly at dose initiation, even in light of available clinical data (Clinical Trial 331-10-242) in which significant signs of QT prolongation have been observed in female patients.

The current RXULTI application is for approval of brexpiprazole as monotherapy in the treatment of schizophrenia. Anyway, concomitant medications are commonly used in schizophrenic patients: *e.g*. antidepressants, anxiolytics. Since pharmacology of brexpiprazole is believed to be mediated by a combination of activities at multiple monoaminergic receptors, the potential for pharmacodynamic drug-drug interactions is to be considered.

Following oral administration, an approximately linear PK profile was observed in rats and monkeys species used in toxicological evaluations. In both rat and monkey a food effect reducing absorption of brexpiprazole was observed (differently from the dog). A gender effect in fed female rats was observed with higher AUC value. In contrast to human bioavailability (95%), brexpiprazole showed low bioavailability in rats (13.6%) and monkeys (31%).

In vitro, brexpiprazole was highly bound to serum protein across species tested (mouse, rat, rabbit, dog, monkey, human). Brexpiprazole was bound predominantly to albumin and α1-acid glycoprotein in human serum. *In vivo* brexpiprazole protein binding in rat and monkey plasma was lower than *in vitro* protein binding; no gender effect in rat and no overall time dependency was observed up to 48 hours. From clinical studies, brexpiprazole bound human plasma protein to 99%.

In vitro, neither warfarin nor diazepam affected brexpiprazole binding to human albumin while digitoxin was able to displace brexpiprazole only at low extent not clinically relevant.
In vitro, DM-3411 protein binding in the monkey and human sera was lower than that of brexpiprazole.

Following oral administration in rats, the concentrations of radioactivity the CNS were generally lower than in plasma and were quantifiable up to 24 hr post-dose in males and up to 8 hr post-dose in females. An uneven brexpiprazole distribution pattern was observed: almost no radioactivity was observed in the white matter. From these results, there was no evidence on the relationship between the cerebral distribution of this drug and the brain lesions (demyelination and necrosis of the oligodendrocytes in the neurotoxicity toxicity studies. The major metabolites DM-3411 was not detected in rat CNS; since no brain distribution study was performed in other species nor in human tissue. It is not possible to exclude a different behavior of DM-3411 in CNS.
Although results in pigmented rats (Long-Evans) suggested brexpiprazole has an affinity for melanin. Brexpiprazole resulted non-phototoxic in albino mice toxicological studies.
Brexpiprazole and its metabolites were transferred into the foetus of pregnant rats at concentrations that were generally comparable to levels seen in maternal blood.

The S-oxide of the benzothiophene structure of brexpiprazole DM-3411 resulted the most abundant brexpiprazole metabolite both *in vitro* and *in vivo* across species except for female rat where DM-3404 was the predominant *in vitro* metabolite. In Human Cytochrome P450s Baculovirus Insect Cell Expressed and in human liver microsomes, brexpiprazole was mainly metabolised to DM-3411 by CYP2D6 and CYP3A4. Brexpiprazole showed a high inhibitory potential to CYP2B6 isoform (Ki=5.01 μM) in human liver microsomes and a small induction potential to CYP1A2, CYP3A4/5 and CYP3A4 activity in primary cultured human hepatocytes.
The biotransformation profile of brexpiprazole was qualitatively similar across species.

DM-3411 did not significantly inhibit several CYP isoenzyme and no induction potential by DM-3411 was assessed. Being pharmacologically active in rat, monkey and human, DM-3411 was fully characterised from the safety point of view.

In both female and male rats and male monkeys unchanged brexpiprazole was eliminated mainly with feces and excretion was almost complete by 168 hr post-dose. No sex differences in excretion of brexpiprazole were noted in rats.

Overall, based on the results from *in vitro* CYP and transporter studies, and clinical DDI studies, the potential for brexpiprazole or DM-3411 to produce systemic drug-drug interactions appears minimal.

Rats and cynomolgus monkeys were used in general dose-repeat toxicity studies. They are considered relevant species for assessment of human safety due to presence of the pharmacological target, and comparable metabolic profile with humans, although the very low exposure reached in monkeys raises concerns.

In all rat studies, there was a largely consistent pattern of observations including decrease in body weight gain and food consumption, incomplete eyelid closure, hypoactivity, lacrimation, creeping, staggering gait, poor physical condition (consistent with the depression of CNS as the brexpiprazole pharmacodynamic effects), hyperreactivity and aggressiveness that might be excessive adaptive-responses to the brexpiprazole-induced depression of CNS.

Clonic convulsions occurred at exposure in term of AUC_{0-24} of about 11 fold higher than that reached in patients receiving the MHRD of 4 mg/kg of brexpiprazole. Although no longer present during the recovery phase of the study, clonic convulsions is judged to be a toxic change in rats due to brexpiprazole exposure. Clonic convulsion/seizure is regarded as a dopamine under activity condition mediated by dopamine antagonist agents (*Starr, 1996*). "Seizure" is considered a potential risk for humans in the RXULTI RMP.
Haematology and clinical chemistry changes induced by brexpiprazole are considered not toxicologically relevant due to their sporadic nature, the absence of a dose-response relationship, small magnitude of change, almost total reversibility, possible association with decreased food consumption and body weight or stress and absence in monkeys and in humans.
Brain lesions were observed in rats at brexpiprazole exposures about 29 and 7 fold higher for males and females respectively.
Spermatogenesis, hypertrophy of corpus luteum, uterus atrophy and mucification, increased ovary weights and increased incidence of lobular hyperplasia with secretion of milk in the mammary gland (pseudopregnancy) and femminization of mammary gland in males observed at high doses, are considered consequences of drug-related pharmacologically mediated hyperprolactinemia.

Similar to studies in the rat, in monkey studies there was a largely consistent pattern of observations linked to brexipirazole pharmacodynamics. Unlike the rat, tremors, limited to the extremities in 4 and 13 week studies and whole body tremors in the 39 week studies, were observed. Tremors are not considered mediated by pharmacological CNS depression. The whole tremors are present at exposures even lower than those observed in patient receiving the therapeutic dose of brexpiprazole, and they are not reversible in females monkeys dosed at exposure 1.3 fold higher that reached in patients. Tremors are one of the signs of EPS a common composite adverse reaction due by antidopaminergic effect of antipsychotics. In short term controlled trials EPS-related TEAEs (mainly driven by akathisia events) higher than placebo was observed only for 4 mg. EPS is an important identified risk in RMP also supported by non-clinical data. Thus the claimed intermediate level of brexpiprazole dopaminergic tone that should allow to remain beneath the threshold development of positive symptoms and avoid adverse effect as EPSs (*Frankel and Schwartz, 2017*) appears not met in clinical settings at higher doses.
Among the EPS, tardive diskinesia is associated with long-term use of antidopaminergic agents and is characterised by irreversibility after removal of the antidopaminergic agent (*Ure et al., 2016*). This is likely mediated by sensitisation of D2 receptors. In pharmacodynamic study 020354, repeated administration of 6 mg/kg brexpiprazole showed at least a comparable potential to enhance sensitivity of postsynaptic D2 receptors than haloperidol.

The genotoxic potential of brexpiprazole was investigated in a bacterial reverse mutagenicity assay, an *in vitro* mammalian mutagenicity assay in L5178Y tk+/- cells and two *in vivo* rat bone marrow micronucleus tests with a two day exposure period and in unscheduled DNA Synthesis Test.

Brexpiprazole was weakly genotoxic at cytotoxic doses *in vitro* Mouse Lymphoma study, however brexpiprazole was negative in the bacterial reverse mutation test and in the *in vivo* genotoxicity tests (bone marrow micronucleus, *in vivo*/*in vitro* unscheduled DNA synthesis).

Although the proposed safety margin for mice and rat carcinogenicity is quite low, both assays are considered overall adequate. In CD 1 mice daily oral gavage administration of brexpiprazole revealed degenerative changes in mammary glands and pituitary in females given >0.75 mg/kg/day without dose related difference. The hyperprolactinemia hypothesis mediated by brexpiprazole dopamine "D2 antagonist effect" for mice female tumours is considered plausible taking also into account that no pattern of change was observed for other hormones linked to mammary tumours, even if some clarification is needed as regards the claimed pharmacodynamics brexpiprazole D2 partial agonist activity. Although the induction of mammary neoplastic lesions by hyperprolactinemia cannot yet be considered definitively an exclusive 'rodent-specific' phenomenon, the role of prolactin in human breast tumours remains unsettled therefore, at this time we have no definitive data suggesting increased risk of breast cancer secondary to hyperpolactinemia caused by antpsychotic, and further prospective studies with large number of patients are considered desirable in this area before a definitive answer can be provided (*Vyas, 2012*). Available clinical data derived only by short-term trials, showed that median prolactin values increased from baseline in the brexpiprazole 2 to 4 mg/day group and were more pronounced in females compared with males and in general the increase in prolactin was not associated with an adverse clinical outcome (i.e., AEs potentially related to prolactin elevation).

Rat male fertility was unaffected up to 100 mg/kg. Prolonged estrus and decreased fertility (pregnancy rate of 80.0% and 78.9%, respectively, as compared with 95.0% in controls) at 3 and 30 mg/kg, were observed in female rats, as well as increased pre-implantation losses at 30 mg/kg (17.7% vs 3.0% in control 3.0%). The NOAEL for female reproduction was 0.3 mg/kg/day (0.3 exposure margins in terms of AUC). Impaired female rat fertility islikely related to the increase serum prolactin induced by brexpiprazole.
Based on results from rat and rabbit embryo-foetal development studies, no clear signs of fetal malformations were observed in brexpiprazole-treated rats when tested up to the approximate clinical AUC exposure (estimation based on TK data in non-pregnant rats). In rabbit, vertebral malformations were seen at exposeure ~16-fold the clinical AUC. These skeletal malformations although seen at a low incidence were not observed in the control group and their incidences are outside the historical control data of the test facility and literature data. In addition, the incidence of the visceral malformation (absence of gall bladder) seen in 2 fetuses of 1 litter is also outside the historical control data and literature data. The "use in pregnancy and lactation" is a missing information in the RMP and the participation in the National Pregnancy Registry for Atypical antipsychotics has been requested to be included in the RMP as an additional pharmacovigilance activity.
Delayed growth, physical development and impaired viability of the offspring were only observed at maternally toxic brexpiprazole doses in a pre-/postnatal development toxicity study in rats.
Fetus and milk transfer of [14C]-brexpiprazole after oral administration to rats, was demonstrated at concentrations that were generally comparable to levels seen in maternal blood.

In the table below a comparison of Cmax and AUC0-24h values for brexpiprazole and the main metabolite DM-3411 at the NOAELs of pivotal toxicology reports vs human exposure at the proposed therapeutic dosage of 4 mg/day (derived from clinical trial report 331-08-205: brexpiprazole Cmax 199 ng/mL and AUC 0-24 3950 ng.h/mL at day 14) and respective exposure multiples, is reported:

Species	Rat		Monkey		Rat (Pregnant)	Rabbit (Pregnant)	Rat		Rat		Mouse		Human
Study Duration	26 Weeks		39 Weeks		EFD	EFD	Fertility		Carcinogenicity				
Gender	Male	Female	Male	Female	Female	Female	Male	Female	Male	Female	Male	Female	-
NOAEL (mg/kg/day)	3	10	1	1	30	30	100	0.3[b]	10[c]	30[c]	5[c]	<0.75[c]	-
C_{max} (ng/mL)													
OPC-34712	91.3	551.3	156.2	165.6	1476[d]	1720	3425[d]	161[d]	418.5	1433	1076	<65.3	199
Margin of Exposure[a]	0.5	2.8	0.8	0.8	7.4	8.6	17.2	0.8	2.1	7.2	5.4	<0.3	-
DM-3411	16.9	87.4	78.1	91.6	303.2[d]	72.0	580.3[d]	32[d]	104.3	259.7	19.0	<6.2	64.3
Margin of Exposure[a]	0.3	1.4	1.2	1.4	4.7	1.1	9.0	0.5	1.6	4.0	0.3	<0.1	-
$AUC_{0\text{-}24h}$ (ng-h/mL)													
OPC-34712	591	3285	1680	1773	16390[d]	23220	45930[d]	1140[d]	3912	17400	12430	<773	3950
Margin of Exposure[a]	0.1	0.8	0.4	0.4	4.1	5.9	11.6	0.3	1.0	4.4	3.1	<0.2	–
DM-3411	103	440.3	640.7	751.9	2123[d]	716.8	4647[d]	195[d]	861.4	2081	246.8	<58.6	1280
Margin of Exposure[a]	0.1	0.3	0.5	0.6	1.7	0.6	3.6	0.2	0.7	1.6	0.2	<0.05	–

$AUC_{0\text{-}24h}$ = area under the concentration-time curve from 0 to 24 hours; C_{max} = maximum concentration; EFD = embryo-fetal development; NOAEL = no observed adverse effect level.

Source: Otsuka Report Nos. 023880 (rat), 024787 (rabbit), 024584 (monkey), 028338 (mouse carcinogenicity), 028376 (rat carcinogenicity). Pharmacokinetic data represent repeat-dose exposure at the end of the dosing period. The pharmacokinetic data for human subject are from Clinical Trial 331-08-205 based on a dose of 4 mg as the maximum recommended human dose.

[a]The margin of exposure was determined as the ratio of exposure (AUC or C_{max} of brexpiprazole or DM-3411) in animals to the exposure in humans.

[b]NOAEL for reproduction (Otsuka Report No. 020004).

[c]NOEL for carcinogenicity.

[d]C_{max} and $AUC_{0\text{-}24h}$ are shown for the dose of 30 mg/kg/day or 3 mg/kg/day (females) and 100 mg/kg/day (males) from Week 13 of the 26-week toxicity study in rats (Otsuka Report No. 023880). Values at 0.3 mg/kg/day were calculated based on data at 3 mg/kg/day.

At NOAEL safety margins based on toxicokinetic exposure data (Cmax and AUC both for parent compound and the main metabolite) are quite low in both chronic rat and monkey reports and in rat and rabbits female fertility studies. In monkeys margins still remains low also at the highest doses.
In the repeated dose toxicity studies in rats and monkeys, brexpirazole-induced effects were generally mild at the low dose levels (male rats 3, female rats 1 mg/kg/day, monkeys 1 mg/kg/day). At these doses, exposure margin in term of AUC does not exist: 0.1 M-0.8 F and 0.4 in male and female rats and monkeys, respectively. More evident effects were observed at the high dose levels where exposure multiples were 11.2 in males and 8.7 in females rats and 1.8 in males and 1.35 in females monkeys, i.e. not in high excess of human therapeutic exposure, especially in monkey. This can be due to the fact that brexpiprazole toxicities observed in mice, rats and monkeys were mainly related to the exaggerated pharmacological activity (e.g. hypoactivity, hypothermia or hyperprolactinemia). Despite this, the studies conducted are considered sufficiently adequate to support the current application taking also into account that histopathological changes other than those related to these clinical conditions and other toxicities were not evident in animals that survived the dosing phase.

Drug substance impurities were chemically and toxicologically qualified.

Brexpiprazole was not considered to be phototoxic in albino mice studies.
As regard the abuse liability/potential, brexpiprazole was considered to possess discriminative stimulus effects in rats but no withdrawal signs suggestive of physical dependence production were evident in rats, nor reinforcing effect in the IV self-administration experiment in rhesus monkeys. No withdrawal signs were recorded in the recovery periods of the rat and monkey repeated dose toxicity studies.

Brexpiprazole is very persistent and very bioaccumulative, but not toxic: possible enrichment of brexpiprazole in terrestrial food chains might pose a concern. This risk is reflected in sections 5.3 and 6.6 of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical aspects of brexpiprazole are considered adequately assessed and supportive of the marketing autorisation of RXULTI in the treatment of schizophrenia in adult patients. The CHMP considers the following measures necessary to address the non clinical issues: The Applicant is committed to perform an OECD 106 study to determine the adsorption of brexpiprazole in three soils and then re-evaluate the ERA once completed.

2.4. Clinical aspects

2.4.1. Introduction

Table 2 Tabular overview of clinical studies

Table 2.5.1.2-1 Overview of All Brexpiprazole Trials in Clinical Development Program

Phase 1 Clinical Pharmacology Trials (N = 29)		Phase 2 and 3 Trials by Indication (N = 27)			Phase 3b Trials by Indication (N = 8)
Healthy Subjects	**Special Populations**	**Schizophrenia**	**MDD**	**Other Indications**	**Schizophrenia**
331-07-201 331-07-202 331-08-206 331-08-207 331-08-208 331-09-224 331-10-239 331-10-240 331-10-241 331-10-243 331-10-244 331-10-245 331-10-246 331-12-207 331-13-209 331-07-002 [J] 331-KOA-0701 [K] 331-10-005 [J]	Hepatically impaired 331-09-225 Renally impaired 331-09-226 **Subjects by Indication** Schizophrenia 331-08-205 331-08-209 [1b] 331-09-219 331-10-242 331-10-001 [J] (331-10-233) MDD 331-09-221 331-12-291 ADHD 331-09-220	Placebo-controlled 331-07-203 [2, MN] 331-10-230 [3, MN] 331-10-231 [3, MN] 331-10-232 [3, MN] 14644A [3, MN] 331-10-002 [2/3, J] Long-term, Open-label 331-08-210 [2, MN] 331-10-237 [3, MN] 14644B [3, MN] 331-10-003 [3, J]	Placebo-controlled 331-08-211 [2] 331-09-222 [2] 331-10-227 [3, MN] 331-10-228 [3, MN] (331-12-282) [3, MN] 14570A [3, MN] 14571A [3, MN] 331-13-214 [3] Long-term, Open-label 331-08-212 [2] (331-10-238) [3, MN] 14767B [3, MN] 16160A [3, MN]	ADHD 331-08-213 [2] Agitation associated with dementia of the Alzheimer's type (331-12-283) [3, MN] (331-12-284) [3, MN] (331-13-211) [3, MN] PTSD 14865A [3, MN]	331-13-006 [3b] 331-13-008 [3b] 331-13-009 [3b] **MDD** 331-13-001 [3b] 331-13-002 [3b] 331-13-003 [3b] 15352A [3b] 15353A [3b]

J = Japan; K = Korea; MN = multinational.
Data shown are trial number, and trial phase and country (if other than US only) in brackets for trials by indication (disease state).
( ) represents a trial that was ongoing at the time of data cut-off for this submission; planned (ie, not initiated) trials are not included.
An additional clinical pharmacology protocol, Trial 331-12-208, is a cross-trial population pharmacokinetic (PK) analysis only with data obtained from a select number of previously completed phase 1 and phase 2 and 3 (schizophrenia and MDD) brexpiprazole trials. This protocol is not included in this table nor in the overall total count of brexpiprazole trials as of the data cutoff date (31 Aug 2016).
Note: Trial 331-10-233 population consists of adolescents with a diagnosis of schizophrenia or other related psychiatric disorders.

Table 2.5.1.3-1 Overview of Brexpiprazole Clinical Program to Establish Efficacy and Safety of Brexpiprazole for the Treatment of Schizophrenia

	Phase 3 Trials					Phase 2 Trial
Trial	**331-10-231**	**331-10-230**	**331-10-002**	**14644A**	**331-10-232**	**331-07-203**
Number of Subjects in Safety Sample						
Brexpiprazole	452	490	342	150	97	314
Placebo	184	184	116	161	104	95
Aripiprazole	0	0	0	0	0	50
Quetiapine	0	0	0	153	0	0
Design	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Double-blind, placebo-controlled with active reference	Double-blind, placebo-controlled	Double-blind, placebo- controlled with active reference
Treatment Duration	6 weeks	6 weeks	6 weeks	6 weeks	Up to 52 weeks	6 weeks
Dosing Schedule	Fixed	Fixed	Fixed	Flexible	Maintenance	Fixed-flexible
Treatment Groups	4, 2, 0.25 mg/day Placebo	4, 2, 1 mg/day Placebo	4, 2, and 1 mg/day Placebo	2 to 4 mg/day Placebo Quetiapine 400 to 800 mg/day	1 to 4 mg/day Placebo	0.25 mg 1.0±0.5 mg/day 2.5±0.5 mg/day 5.0±1.0 mg/day Placebo Aripiprazole (15±5.0 mg/day)
Randomization Ratio	2:2:2:1	3:3:2:3	1:1:1:1	1:1:1	1:1	1:2:2:2:2:1
Primary Endpoint	Change in PANSS Total Score at Week 6 (MMRM)	Change in PANSS Total Score at Week 6 (MMRM)	Change in PANSS Total Score at Week 6 (MMRM)	Change in PANSS Total Score at Week 6 (MMRM)	Time From Randomization to Impending Relapse	Change in PANSS Total Score at Week 6 (LOCF)
Key Secondary Endpoint	Change in CGI - S Score at Week 6	Change in CGI - S Score at Week 6	NA[a]	Change in CGI - S Score at Week 6	Percentage of Subjects Meeting Impending Relapse Criteria	Change in PANSS Positive, PANSS Negative, PSP, and CGI - S Score, at Week 6

CGI-S = Clinical Global Impression - Severity of Illness scale; LOCF = Last observation carried forward; MMRM = Mixed model repeated measure; NA = not applicable; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance scale; SCE = Summary of Clinical Efficacy.

[a]In Trial 331-10-002 protocol, no key secondary endpoint is defined; CGI-S is listed as a secondary endpoint. In the SCE, CGI-S from Trial 331-10-002 is included in the analysis of the key secondary endpoint, in order to allow a comparison across trials.

2.4.2. Pharmacokinetics

Brexpiprazole (OPC-34712, OPC-331, and Lu AF41156) is a new chemical entity developed for treatment of schizophrenia (and other psychiatric disorders) in adult patients. The pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors.
The maximum daily brexpiprazole dose is 4 mg per day. In order to reduce the risk of undesirable effects, the recommended target dose is achieved by upward titration after the initial 1 mg per day dose during the first 4 days. The recommended target dose range is 2 mg to 4 mg per day. Increase dose to 2 mg per day on Day 5 through Day 7, then to 4 mg per day on Day 8 based on the patient's clinical response and tolerability. The recommended target dose range is 2 mg per day to 4 mg per day.

Analytical methods
A summary of the analytical methods supporting brexpiprazole PK evaluation is provided below.

Table 3 Bioanalytical Methods Used in Clinical Trials

Table 2.7.1.1.4-1 Bioanalytical Methods Used in Clinical Trials					
Report	**Trials**	**Method**	**Matrix**	**Validated Analyte(s)**	**Linearity**
Report 6825–271, 5.3.1.4	331-07-201 (Arm 1) 331-07-201 (Arm 2)[a] 331-07-201 (Arm 3)[a] 331-07-202, 331-08-205 331-08-206, 331-08-207 331-08-208, 331-09-219 331-09-224, 331-09-225 331-09-226, 331-10-239 331-10-240, 331-10-241[a] 331-10-242, 331-10-243[a] 331-10-244, 331-10-245[a] 331-10-246[a], 331-12-291 331-08-209, 331-09-220 331-09-221, 331-07-203 331-08-211, 331-08-213 331-09-222, 331-10-227 331-10-228, 331-10-230 331-10-231, 331-10-232 331-12-207, 331-13-209	C_{18} reversed-phase HPLC-MS/MS	Plasma	Brexpiprazole and 7 metabolites	0.300–100 ng/mL
Report 6825–263, 5.3.1.4	331-07-201 (Arm 1)	C_{18} reversed-phase HPLC-MS/MS	Plasma	Brexpiprazole and DM-3411	0.300–100 ng/mL
Report 6825–273, 5.3.1.4	331-07-201 (Arm 1) 331-07-201 (Arm 2)[a] 331-08-206 331-09-225 331-09-226	C_{18} reversed-phase HPLC-MS/MS	Urine	Brexpiprazole and 7 metabolites	0.600–200 ng/mL
Report 6825–284, 5.3.1.4	331-07-201 (Arm 2)[a]	C_{18} reversed-phase HPLC-MS/MS	Feces	Brexpiprazole	1.00–1000 ng/mL
Report 15657, 5.3.1.4	14644A	C_{18} reversed-phase HPLC-MS/MS	Plasma	Brexpiprazole and DM-3411	1.00–100 ng/mL

HPLC-MS/MS: high-performance chromatography with tandem mass spectrometry.
[a] Bioavailability or biopharmaceutic trial.

As general comment, analytical methods supporting brexpiprazole PK evaluation, were correctly developed and validated.

Biopharmaceutics

The mean absolute bioavailability of brexpiprazole oral tablets was 95.1%. Brexpiprazole, is considered to be a BCS Class II compound, *i.e.* a high Permeability, low Solubility drug, according to the Biopharmaceutics Classification System (BCS) Guidance.

Initially, 0.05 mg, 0.25 mg, 1 mg, and 5 mg brexpiprazole tablet strengths were developed and used in the majority of phase 1 clinical trials. For phase 3 safety and efficacy trials, additional brexpiprazole tablet dose strengths (0.5 mg, 2 mg, 3 mg, and 4mg tablets) were developed. The planned marketed (commercial) brexpiprazole tablets are 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg dose strengths.

Brexpiprazole tablets intended for commercial use are identical to the tablets developed for the Long Term Stability Studies (LTSS) in terms of dose strengths (0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg), method of manufacturing, manufacturing scale, colorant, composition and debossing (LTSS tablets included dummy debossing). Thus, the Commercial tablets, hereafter, are referred to as LTSS/Commercial tablets.

Bioavailability studies demonstrated that: the 3 mg LTSS/Commercial tablet is bioequivalent to the 3 mg P3 Clinical tablet (study 331-13-209) and 3 x 1 mg P2 Clinical tablets (study 331-10-243); the 2 mg LTSS/Commercial tablet is bioequivalent to 2 x 1 mg P2 Clinical tablets (study 331-10-243); and the 4 mg LTSS/Commercial tablet is bioequivalent to 4 x 1 mg P2 LTSS/Commercial tablets (study 331-10-245).
In trial 331-13-209, 3 mg tablets were used to determine bioequivalence between the commercial and clinical tablets to support the request for a strength biowaiver. However, the applicant has applied for 0.25, 0.5, 1, 2, 3 and 4 mg tablets in this marketing authorisation. The applicant has discussed the rational for investigating the 3 mg, as this was triggered by results form the dissolution testing, ad it is agreed that a bioequivalence study of the 4 mg dose is not required.A high-fat meal does not affect the rate and extent of absorption of orally administered brexpiprazole at the highest dose of 4 mg commercial brexpiprazole tablet (Trial 331-10-246) or 2 mg P2 Clinical tablets (Trial 331-07-201). Solubility of brexipiprazole is pH dependent, being highly soluble at acid pH, however administration with 40 mg omeprazole did not affect the Cmax of brexipiprazole however there was 22% and 18% increase in AUC_T and AUC_∞, respectively. This increase in exposure does not appear to be clinically significant.

Pharmacokinetics
Clinical pharmacokinetic data have been obtained from 28 clinical pharmacology trials. Data from 4 studies conducted in Korea and Japan (1 in healthy subjects, 1 in patients with schizophrenia) have been provided but not used to support this application.

A summary of PK studies is shown in the Table reported below.

Table 4 Summary of Brexiprazole Clinical Pharmacology Trials with Brexpiprazole Oral Tablets

Table 2.7.2.1.1-1 Summary of Brexpiprazole Clinical Pharmacology Trials with Brexpiprazole Oral Tablets			
Trial Number	**Subjects**	**Description**	**Dose(s) [a] (mg)**
Safety and Tolerability			
331-07-201 Arm 1	Healthy	Single rising-dose, safety, tolerability, and PK	0.2, 0.5, 1, 2, 4, 6, 8
331-08-206	Healthy	Multiple rising-dose safety, tolerability, and PK	0.5, 1, 2, 3
331-08-205	SCHZ	Multiple rising-dose safety, tolerability, and PK	1, 2, 4, 6, 8, 10, 12
331-09-221	MDD	Multiple-dose safety, tolerability, and PK	1.5, 2, 3, 4
331-09-220	ADHD	Multiple-dose safety, tolerability, and PK	3, 4
331-12-291	MDD	Multiple-dose safety, tolerability, and PK in elderly	2, 3
Mass Balance, Metabolism, and Excretion			
331-07-201 Arm 2	Healthy	Single-dose, mass balance of ^{14}C-brexpiprazole	2
Absolute Bioavailability			
331-10-241[b]	Healthy	Single-dose absolute bioavailability of oral tablet	2 (oral), 0.25 (IV)
Food Effect			
331-10-246[b]	Healthy	Definitive single-dose food-effect (high-fat meal)	4
331-07-201 Arm 3[b]		Pilot single-dose food-effect (high-fat meal)	2
Drug-Drug Interaction			
331-08-207	Healthy	Effect of CYP3A4 (ketoconazole), CYP2D6 (quinidine), and CYP2B6 (ticlopidine) inhibition on brexpiprazole; Effect of brexpiprazole on CYP3A4 (lovastatin), CYP2D6 (dextromethorphan), CYP2B6 (bupropion) and MDR1 (P-gp) (fexofenadine) substrates	2
331-08-208		Effect of CYP3A4 (ketoconazole), CYP2D6 (quinidine), and CYP2B6 (ticlopidine) inhibition on brexpiprazole	2
331-09-224		Effect of CYP3A4 induction (rifampin) on brexpiprazole	4
331-10-239		Effect of oral activated charcoal with sorbitol on brexpiprazole	2
331-10-240		Effect of increased gastric pH (omeprazole) on brexpiprazole	4
331-12-207		Effect of brexpiprazole on BCRP efflux transporter (rosuvastatin)	6
Intrinsic Factor			
331-09-225	Healthy	Effect of hepatic impairment (mild, moderate, and severe)	2
331-09-226	Healthy	Effect of severe renal impairment	3
331-10-244	Healthy	Effect of age and gender on brexpiprazole	2
Bioequivalence			
331-10-243[b]	Healthy	Bioequivalence of LTSS/Commercial and phase 2 clinical tablets	2, 3
331-13-209[b]		Bioequivalence of LTSS/Commercial and phase 3 clinical tablets	3
331-10-245[b]		Dose-strength equivalence of LTSS/Commercial tablets	4

5-HT$_{1A/2A}$: 5-hydroxytryptamine serotonin 1A/2A; ADHD: Attention-deficit hyperactivity disorder; BCRP: breast cancer resistance protein; CYP: cytochrome P450; IND: investigational new drug; IV: intravenous; LTSS: Long-Term Stability Studies; MDD: major depressive disorder, MDR: multi-drug resistance gene; PD: pharmacodynamics; PET: positron emission tomography; P-gp: P-glycoprotein; PK: pharmacokinetic; SCHZ: schizophrenia; SERT: serotonin transporter; TQT: thorough QTc trial; US: United States.

[a] Brexpiprazole doses were administered orally, unless otherwise noted, and were administered once daily in the multiple-dose trials.

[b] These trials were discussed in 2.7.1.

Absorption

Brexpiprazole is rapidly absorbed with an overall median T_{max} of approximately 4 hours post single dose on Day 1 and of approximately 3 hours after multiple dose on Day 14. The plasma exposure of brexpiprazole after once-daily single- (0.2 mg to 8 mg) and multiple-dose (0.5 mg to 4 mg) increased approximately dose proportionally. The steady-state is reached after 10 to 12 days of daily dosing administration, in line with its half-life of about 90 hrs after multiple dose administration. The accumulation ratio after Day 14 following multiple dose daily administration seems also consistent with the elimination half-life of the compound.

Distribution

Brexpiprazole and DM-3411 are highly protein bound: more than 99% for brexpiprazole and more than 96% in human serum for DM-3411. In human serum, brexpiprazole is bound predominantly to albumin and α1-acid glycoprotein in human plasma, and is not affected by warfarin, diazepam, or digitoxin, nor is it altered in patient s with hepatic or renal impairment. From the population PK model, the apparent volume of distribution (V/F) in the central and peripheral compartments was estimated to be 105 L and 28.4 L respectively. In the responses to LoQ D120 the Applicant also provide a summary statistics of the estimated appartent volume of distribution (V/F) form single dose trial (127 L, SD 95.3).

Elimination

After single oral dose (0.2 mg to 8 mg) administration the mean half-life was 79.3 hours and 73.6 hours for brexpiprazole and DM-3411, respectively. After multiple, once daily administration (1 mg to 12 mg), the mean half life was 91.4 and 85.7 hours for brexpiprazole and DM-3411 respectively. A mass balance was performed in 16 healthy male subjects. The brexpiprazole dose was a combination of non-radiolabelled (2 mg) and radiolabelled compound (microdose tracer amount, <270 nCi) with 14C -brexpiprazole radiolabel inserted in either the quinolinone (8 subjects) or benzothiophene ring (8 subjects). Samples were collected for up to 20 days (480 hours) after dosing. Hepatic clearance is the major route of elimination of brexpiprazole followed by renal clearance.

Excretion

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%). The total radioactivity recovery was low (71.1%). The applicant has qualified brexpiprazole, DM-3411, and DM-3412, MOP-54522 OPC-54050, OPC-34835 and OPC-3952 in plasma (SFO-34318 was not quantified) following 14 days of dosing in subjects with schizophrenia (CSR 331-08-205). Furthermore, the applicant has performed sparse sampling in late phase studies and quantified brexpiprazole and DM-3411 in these studies. However, the applicant has not addressed the potential accumulation of the metabolites; while the metabolites (apart from DM-3411) appear to have minimal contribution to the primary effects of brexpiprazole, this does not negate any off-target effects if there is accumulation. Most brexpiprazole elimination is due to faecal excretion followed by urine excretion. The percentages of unchanged brexpiprazole recovered in urine and faeces form less than 1% and 14% of the dose administered, respectively.

The little amount (<1%) of unchanged brexpiprazole recovered in the urine indicates that the large majority of the administered dose is metabolised.

Metabolism

Results from ADME study showed that brexpripazole is extensively (>97%) metabolised in humans. Less than 1% of unchanged brexipripazole could be detected in urine. The predominant human CYPs concerned with metabolism of brexpiprazole were identified as CYP2D6 and CYP3A4. The contribution of

CYP3A4 and CYP2D6 metabolic pathway to the total apparent CL of brexpiprazole is estimated to be 46.7% and 43.3% and about 10% attributed to other minor pathways [*i.e.,* flavin-containing monooxygenases (FMO3)]. Other CYPs that contribute to brexpiprazole include CYP2B6, CYP2C19, CYP1A1. The main metabolite identified was DM-3411, in human studies, the metabolites OPC-3952, SFO-34318, DM-3411, DM-3404, DM-341, DM-3413, MOP-54522, and OPC-34835, were observed in urine.
Brexpipraxole has a maior circulating metabolite (>10%); metabolite DM-3411. PK parameters of metabolite DM-3411 were evaluated in all single and multiple dose phase I and phase II studies. The Applicant claimed that this metabolite is not considered pharmacologically active, however the non clinical review of data showed that it is a potent antagonism activity to hD2Short (IC50<5 nM). DM-3411 brain penetration has been shown to be poor based on a non-clinical study in rats administered high doses of radiolabelled brexpiprazole.

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. The metabolite-to-parent ratio of DM-3411 and DM-3412 metabolites was similar across trials and following single- and multiple-dose administration.

In study 331-08-208, comparison of the AUC values in subjects in Group 4 (poor metabolizers of CYP2D6 isozyme) to the subjects in Groups 1 through 3 (extensive metabolizers of CYP2D6 isozyme) indicates that brexpiprazole exposure was about two-fold higher in poor metabolizers of CYP2D6; however, no definitive information can be drawn from this study due to the limited number of subjects. The effect of CYP2D6 poor metabolism has been further evaluated in a larger population and as a component of the population PK analysis
The effect of CYP2D6 metabolism status (poor, intermediate, and ultra-rapid relative to extensive) on CL/F was included as significant covariate in the final PopPK model (considering the inferred CYP2D6 metabolic status among subjects included in the popPK analysis, 3% were PM, 24% IM, 38.7% EM, 1.4% UR, and 33% were missing/inconclusive).
In subjects who are poor (PM), intermediate (IM) and ultra-rapid (UR) CYP2D6 metaboliser, CL/F was estimated to be -32%, -20% and +18%, respectively when compared to the value estimated for extensive (EM) CYP2D6 metabolizer subjects, corresponding to a +47%, +25% and -21%, change in brexpiprazole exposure (AUC_T), respectively. Dose adjustment of half of the label-recommended maintenance dose is recommended in patients with poor CYP2D6 metabolism status and the necessity of a mandatory genotyping assay should be discussed by the applicant. The percentages of UR, EM, IM and PM are highly comparable among the three pivotal studies (331-10-002, 331-10-230 and 331-10-231).

For brexpiprazole and DM-3411 there was a proportional increase in exposure (Cmax, AUC_T, or AUC) with increases in dose. Inter-subject variability for brexpiprazole was 19.0%–32.0% for Cmax and 40.0%–55.0% for AUC_∞. Intra-individual variability (residual proportional error in the population PK model) for brexpiprazole was 3.7% and 3.2% for the phase 1 and phase 2/3 data, respectively. Intra-subject variability based on BE studies was 11.9%–16.0% for Cmax and 10.8%–14.6% for AUC_∞.

Population PK
A 2-compartmental population PK model was developed for oral brexpiprazole. The population PK analysis was performed including a total of 2654 quantifiable brexpiprazole plasma concentrations from 154 healthy subjects and 3114 quantifiable plasma brexpiprazole concentrations from 1140 subjects

with MDD and 5072 PK samples from 1247 schizophrenia subjects (2541 total subjects) were available for the population PK analysis. The evaluable dataset included 2357 subjects, who had at least one measurable brexpiprazole concentration.
Parameters estimates in the final model were: CL/F (1.65 L/hr), Q/F (0.701 L/hr), Vc/F (105 L), Vp/F (28.4 L) and ka (0.635h-1).Shrinkage was acceptable for CL/F (5.3%) and Vc/F (23%) but high for ka (58%), boot strapping and other diagnotic plots including pcVPC and GOF plots indicated a fair description of the data by the model however, the model underestimated the absorption phase. A bioavailability scaling factor was required for the subjects with MDD possibly due to non-compliance in these subjects. Covariates identified included age on Vc/F, weight om Vc/F, sex on CL/F and Vc/F and CYP2D6 genotype on CL/F.
Regarding population pharmacokinetic analysis, the applicant has provided the pcVPCs stratified for each covariate. Is is agreed that there is general agreement between the observed and predicted data, except where there is limited data i.e., for CYP2D6 poor and ultra-rapid metabolisers. The observed underprediction of AUCt, especially following single-dosing, is recognised by the applicant. However, it is agreed that the broad conclusions following of comparing the AUCs between the different populations of interest can be maintained. The applicant has further discussed the approach taken for choosing the final model exponents and justified this against the approach of using fixed exponents. The model appears adequate and using the final derived model exponents (vs fixed exponents) has minimal impact on the simulations.

Special populations
A dedicated study, study 331-09-226, was performed to determine the effect of renal impairment on the pharmacokinetics (PK) of brexpiprazole following a single 3 mg oral dose. This study was a single-dose, open-label, parallel-group, matched trial with a reduced design, evaluating the pharmacokinetics of brexpiprazole in subjects with normal renal function and renally impaired subjects (subjects with severe renal impairment).
The applicant performed a study in subjects with severe renal impairment, following a reduced design. The study showed an increased exposure of 68% in patients with severe impairment following 3 mg dose. On the basis of these study results, the Applicant proposes a maximum dose of 3 mg in these patients and also in patients with moderate renal impairment (not studied).
Although a study with a full design would have provided more precise information, the applicant justification to apply the same dose limitation (3 mg) for safety reasons, also for moderate renal impairment, seems acceptable.

Additionally, the effect of mild and moderate renal impairment was evaluated in the popPK analysis. In the popPK analysis, a 22% increase in brexpiprazole exposure was observed in severe, a 13% increase in moderate and a 5% increase in mild renal impairment
As already observed by the applicant there is a discrepancy in the percentage of increased exposure in between study 331-09-226 and popPK analysis, probably because the popPK did not account for the concomitant reduced hepatic clearance and CYP activity observed in subjects with severe renal impairment.
This explanation is accepted, and considering the more informative data for dose recommendation in subjects with renal impairment as those form study 331-09-226.

Study 331-09-225 was performed to evaluate the pharmacokinetics (PK) of brexpiprazole in subjects with normal hepatic function and subjects with varying degrees of hepatic impairment (mild, moderate, and severe). This was a single-dose, open-label, parallel-group, matched trial evaluating the

pharmacokinetics of brexpiprazole in subjects with normal hepatic function and hepatically impaired subjects after a single oral 2 mg dose of brexpiprazole.
Brexpiprazole AUC increase by 24%, 60%, and 8% in subjects with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic functions. This unclear effect on brexpiprazole AUC (60% increase in hepatic function moderately impaired subjects compared to 8% increase in severe ones) is probably due to the small number of subjects in each group. It is noted that AUC_{inf} of total and unbound ($AUC_{inf,u}$) brexpiprazole is lower in SEVERE Matched Normal Hepatic Function Group: AUC_{inf} =788 ng*h/ml and $AUC_{inf,u}$ =3.63 ng*h/ml when compared to the MODERATE and MILD Matched Normal subgroup where the AUC_{inf} equal 1345 and 1393 ng*h/ml respectively and $AUC_{inf,u}$ equal 5.62 and 5.85 respectively ng*h/ml respectively. The applicant, as requested, provides additional comments and plausible explanations regarding the observed unclear effect of different degrees of hepatic impairment on brexpiprazole AUC (60% increase in hepatic function moderately impaired subjects compared to 8% increase in severe ones).
In subjects with moderate hepatic impairment, the increase of brexipripazole AUC (60%) is in line with the decreased CL due to the decrease hepatic function. In subjects with severe hepatic impairment the absence of a change in brexpiprazole exposure (AUC increase by 8% only) may be due to counteracting mechanisms (reduced hepatic clearance and reduced bioavailability/increased apparent Vd/F) which cancel each other out.
Moreover, decrease in total brexipiprazole Cmax by 55% and increase in the t1/2 by about 50% when compared to matched normal subjects are indicative of increased Vd/F and reduced hepatic CL. A trend in decrease of brexpiprazole Cmax of total and unbound (Cmax,u) brexpiprazole was observed across different degree of hepatic impairment. The Applicant was requested to further discuss the possible causes of this decrease in the Cmax, and comment on the possible reason why in the MILD Matched Normal Hepatic Function Group, the Cmax of total and unbound (Cmax,u) brexpiprazole value is significantly higher: Cmax= 26.7 ng/mL and Cmax,u =0.114 ng/mL compared to the MODERATE and SEVERE Matched Normal subgroup where the Cmax equal 19.3 and 17.7 ng/mL and Cmax,u equal 0.0779 and 0.0760 ng/mL, respectively. The Applicant, as requested, further discuss on a possible explanation for the effect of hepatic impairment on brexpiprazole absorption. The Cmax decrease is probably due to a possible counteracting mechanisms (reduced hepatic clearance and reduced bioavailability/increased Vd/F).
In the SmPC section 4.2 where it is stated: "*The maximum recommended dose in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) is 3 mg once daily*" as this adjustment considers the AUC increase but not the Cmax decrease. The recommended dose adjustment in patients with moderate hepatic impairment is based on the observed exposure changes in this group (AUC increase by 60%) and the applicant proposal to apply the same dose limitation also for subjects with severe hepatic impairment is deemed acceptable
The systemic exposure of brexpiprazole in female subjects was approximately 40% to 50% higher (Cmax and AUC∞) compared with male subjects. The population PK estimated that females would have a 25% higher brexpiprazole exposure (AUC_T).
Race (Caucasian, Black or Asian) was not identified as a covariate in brexpiprazole PK parameters in the population PK model.
Weight was a significant covariate in the population PK model, however that difference between the 5th and 95th percentiles (53.5 kg and 118.6 kg) on the apparent central volume of distribution was less than 20% (-11% to +14%).
There does not appear to be a significant difference in the PK of brexpiprazole in the elderly compared to subjects <65 years of age. Pharmacokinetic data are available for an adolescent population but no other paediatric patients. These data in adolescents have not been reviewed as the indication is for adults only. The applicant has a paediatric investigation plan for brexpiprazole for the treatment of

schizophrenia in children, with a waiver for the paediatric population from birth to less than 13 years of age (EMA decision P/0234/2016).
CYP2D6 status was a statistically significant covariate for CL/F; CL/F of poor and intermediate CYP2D6 metabolizers were estimated to be 32% and 20% lower (47% and 25% higher AUC_{tau}) in these subjects compared with CYP2D6 EM subjects. Dose adjustment of half of the label-recommended maintenance dose is recommended in patients with poor CYP2D6 metabolism status.

Drug-Drug interactions.

In vitro
In vitro studies demonstrated that brexpiprazole and the metabolite DM-3411 were not inhibitors of the CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 or the transporters MDR1 (P-gp), OAT1, OAT3, OCT2, MATE1, MATE2-K, OATP1B1, OATP1B3, and OCT1 at clinically relevant concentrations. *In vitro* studies demonstrated that brexpiprazole1A2, 2C9, 2B6, and 3A4. *In vitro* studies identified brexpiprazole as a potential inhibitor of BCRP. Brexpiprazole does not appear to be a substrate for MDR1, BCRP, OATP1B1, OATP1B3, and OCT1 at a ^{14}C-brexpiprazole concentration of 1 µM.
Regarding *in vitro* interactions and as requested, the applicant has provided a justification for only performing the incubation for 48 hours, namely that phenobarbital lead to an adequate increase in CYP2B6 mRNA levels. The CYP inhibition studies investigating whether the metabolite DM-3411 causes mechanism based inhibition was provided. Given the lack of effect on the probes for CYP3A4, 2D6 and 2B6 enzymes following brexpiprazole dosing for 8 days, mechanism-based is unlikely.
The applicant considers that since DM-3411 is produced by human liver microsomes it is likely to be involved in the *in vitro* induction studies utilising brexpiprazole as a perpetrator.

Population PK analyses were utilized to determine the effects of coadministration of strong CYP3A4 and strong CYP2D6 inhibitors with brexpiprazole (dual inhibition). Compared with CYP2D6 EM subjects simulated AUC_T was:
- 1.8-fold higher in CYP2D6 EM subjects co-administered strong CYP3A4 inhibitors;
- 4.8-fold higher in CYP2D6 PM subjects co-administered strong CYP3A4 inhibitors; and
- 5.1-fold higherCYP2D6 EM subjects co-administered strong CYP2D6 inhibitor (fluoxetine and paroxetine) antidepressants and strong CYP3A4 inhibitors (dual inhibition). Dose adjustment in these subjects is recommended.

Taking into account the consistency between observed data (with one inhibition) and simulations and also considering that the popPK model used for such simulation was well validated internally and externally, in principle dose reduction to one quarter (25%) in case of co-administration of strong CYP3A4 and strong CYP2D6 inhibitors with brexpiprazole (dual inhibition) is acceptable. VPCs plots generated using data from DDI study 331-12-208 (with CYP2D6 and CYP3A4 inhibitors) were provided. Model predicted concentrations were consistent with the observed data.

In vivo
Brexpiprazole as victim
In vivo DDI studies were performed to evaluate the effects of other drugs on brexpiprazole PK parameters and *vice versa*.
In study 331-08-208 the co-administration of a strong CYP3A4 inhibitor (ketoconazole, 200 mg twice daily for 6 days starting from day 14) with brexpiprazole (2 mg single dose administered without inhibitors (Day 1) and with inhibitors (Day 14)) resulted in similar brexpiprazole Cmax. Brexpiprazole

AUCt and AUCinf were 59% (GMR: 1.59, 90% CI: 1.44-1.75) and 97% (GMR: 1.97, 90% CI: 1.63-2.37) higher, respectively, and t1/2 was about 50% longer with ketoconazole.
Co-administration of a strong CYP2D6 inhibitor (quinidine, 324 mg dose of quinidine gluconate extended release once daily, for 6 days starting from day 14) with brexpiprazole (2 mg single dose administered without inhibitors (Day 1) and with inhibitors (Day 14)) resulted in similar brexpiprazole Cmax. Brexpiprazole AUCt and AUCinf were 63% (GMR: 1.63, 90% CI: 1.34-1.97) and 94% (GMR: 1.94, 90% CI: 1.49-2.53) higher, respectively and t1/2 was about 50% longer with quinidine.
Co-administration of a strong CYP2B6 inhibitor (ticlopidine, 250 mg twice daily) did not result in significant changes in the brexpiprazole PK (C_{max} and AUC).

Based on the results of these DDI trials, CYP3A4 and CYP2D6 were identified to be primarily responsible for the metabolism of brexpiprazole. Dosage adjustment to one-half of the target dose is recommended in subjects who are taking concomitant strong CYP3A4 inhibitors or CYP2D6 inhibitors.

Results from Study 331-09-224 showed that co-administration of a strong CYP3A4 inducer (rifampin, 600 mg once daily) with brexpiprazole (4 mg) resulted in 31% and 73% lower brexpiprazole Cmax and AUC∞, respectively. For DM-3411, co-administration with rifampin resulted in Cmax values being reduced by 50%, AUCt and AUC∞ were similar/slightly decreased. These results suggest that DM-3411 is formed and metabolised by the CYP3A4.

The applicant has simulated the effect of coadministration of a CYP3A4 inducer on the PK of brexpiprazole, based on the clearance observed in the DDI study. Simulations of 12 mg once daily, 16 mg once daily, 6 mg twice daily and 8 mg twice daily administration of brexpiprazole were provided by the applicant. On the basis of the submitted simulations the SmPC sections 4.2, and 4.5 have been amended to reflect that if brexpiprazole is used concomitantly with strong CYP3A4 inducers (e.g. rifampicin), the total daily dose requirement of brexpiprazole is increased by approximately a factor of three at steady state. Once daily dosing results in high peak to trough fluctuation, hence twice daily divided dosing is preferable from a PK perspective.

Brexpiprazole as perpetrator
In vivo studies indicate that brexpiprazole does not change the PK of lovastatin (a CYP3A4 substrate), bupropion, (a CYP2B6 substrate), and fexofenadine (a P-gp substrate) with no changes in Cmax or AUCт. Brexpiprazole did not alter the Ae48h dextromethorphan/dextrorphan ratio indicating brexpiprazole is not a 2D6 inhibitor.

Administration of rouvastatin (a BCRP transporter substrate) with brexpiprazole resulted in similar AUCt and AUC∞ but 24% lower Cmax values for rouvastatin compared to rouvastatin alone. In a secondary analysis, similar results were observed when only healthy subjects homozygous for c.421CC were analysed.
In the SmPC, the applicant states that 'brexpiprazole does not affect absorption of medicinal products that are substrates of BCRP transporter (rosuvastatin) and Pgp transporter (fexofenadine). This statement does not fully reflect the findings of the clinical studies, given the minimal impact of brexpiprazole on the PK of the BCRP transporter, rosuvastatin, however this issue is not pursued.
Omeprazole is a CYP2C19 inhibitor (and a CYP1A2 inducer), while CYP2C19 metabolism is a known albeit minor metabolic pathway between brexipiprazole and DM-3411. Administration of brexpiprazole with omeprazole (Study 331-10-240) does not affect its rate or extent of absorption as the GMR and 90% CI for Cmax and AUC PK parameters were within the pre specified equivalence limits of 0.50 to 2.00, however, the Applicant was requested to discuss clinical relevance of apparent decrease in the

exposure (Cmax) of DM-3411 observed in the omeprazole interaction study. The Applicant has recognised that CYP2C19 may be involved in the higher brexpiprazole and lower DM-3411 exposure caused by omeprazole, however has concluded this is not clinically relevant.

331-09-226	Healthy	Effect of severe renal impairment	3
331-10-244	Healthy	Effect of age and gender on brexpiprazole	2
Bioequivalence			
331-10-243[b]	Healthy	Bioequivalence of LTSS/Commercial and phase 2 clinical tablets	2, 3
331-13-209[b]		Bioequivalence of LTSS/Commercial and phase 3 clinical tablets	3
331-10-245[b]		Dose-strength equivalence of LTSS/Commercial tablets	4

5-$HT_{1A/2A}$: 5-hydroxytryptamine serotonin 1A/2A; ADHD: Attention-deficit hyperactivity disorder; BCRP: breast cancer resistance protein; CYP: cytochrome P450; IND: investigational new drug; IV: intravenous; LTSS: Long-Term Stability Studies; MDD: major depressive disorder, MDR: multi-drug resistance gene; PD: pharmacodynamics; PET: positron emission tomography; P-gp: P-glycoprotein; PK: pharmacokinetic; SCHZ: schizophrenia; SERT: serotonin transporter; TQT: thorough QTc trial; US: United States.

[a] Brexpiprazole doses were administered orally, unless otherwise noted, and were administered once daily in the multiple-dose trials.

[b] These trials were discussed in 2.7.1.

2.4.3. Pharmacodynamics

Pharmacodynamics of brexpiprazole has been relatively poorly described in the dossier. The receptor binding profile has been characterised as having modulatory activity at the serotonin (5-HT) and dopamine (D) systems that combines partial agonist activity at serotonergic 5-HT1A and at dopaminergic D2 receptors with antagonist activity at serotonergic 5-HT2A receptors, with similar high affinities at all of these receptors and antagonist activity at noradrenergic α1B/2C receptors. The mechanism of action has also been insufficiently described as possibly correlating to the 5-HT1A/D2 receptor partial agonist activity in combination with 5-HT2A and α1B/2C receptors antagonism and since this is a new compound a full and well informed discussion on presumed mechanism of action was requested to the Applicant. The applicant has provided the requested information. While it mainly consists of hypothetical inferences, it is broadly based on the known pharmacology and therefore valuable.Detailed analysis of primary pharmacology has been conducted through the Studies 331-07-202 (A Phase 1, Open-Label, Positron Emission Tomography (PET) Study in Healthy Subjects Following a Single Oral Dose of OPC-34712) and 331-09-219 (A Multiple Dose Positron Emission Tomography study). The results from these studies confirm the affinity of brexpiprazole to dopamine and 5HT receptors.

Study 331-07-202 was conducted to determine the degree of striatal dopamine D2/D3 receptor occupancy after single dose brexpiprazole administration (0.25 mg, 0.5 mg, 1 mg, 2 mg, 4 mg, 5 mg, or 6 mg) in healthy subjects.

According to this study results, brexpiprazole Cmax and AUC PK parameters as well as mean D2/D3 receptor regional occupancy increased accordingly to brexpiprazole doses. Additionally, plasma brexpiprazole concentration up to ~64 ng/mL (reached after 6 mg brexpiprazole administration) corresponded to more than 80% (Omax=89.2%, EC50=8.13 ng/mL) and 90% (Omax=95.4%, EC50=7.75 ng/mL) dopamine D2/D3 receptor occupancy in the putamen and caudate nucleus, respectively.

Study 331-09-219 assessed D2/D3, 5-HT2A, 5-HT1A, and SERT occupancies at steady state for low (1 mg/day) and high (4 mg/day) brexpiprazole doses for 10 consecutive days in patients with schizophrenia.

A higher receptor occupancy was observed following treatment with brexpiprazole 4 mg/day vs 1 mg/day (67% vs. 27% for D2 and 45% vs. 28% for 5-HT2A, respectively). D3 receptors resulted bound only upon administration of brexpiprazole 4 mg/day (31%). Negligible occupancy was detected at 5-HT1A receptors and SERT (both tested at 4 mg/day only), although no definitive assumptions can be drawn for SERT considering the anomalous PK data concerning patient cohort 3 vs. cohort 1, both of which received brexpiprazole 4 mg/day.
According to the EC50-only model, it appears that brexpiprazole would be moderately D2-preferring (EC50=68 ng/mL) as compared to other receptors (EC50=313 and 92 ng/mL for D3 and 5-HT2A receptor, respectively).
Considering the brexpiprazole single dose-linked PK/PD modelling results from study 331-07-202 and the steady state PK parameters after brexpiprazole multiple dosing (study 331-08-205), it appears that multiple-dose, once-daily administration of brexpiprazole from 1 to 2 mg would be suitable to reach the Omax values observed in study 331-07-202 and, thus, worth pursuing to be further studied in schizophrenia treatment. In study 331-07-202, PET scans (n=3 sans for each subjects) were performed 4 hours post dose (Cmax) and 23.5 hours post dose that represents the Ctrough concentration, considering a once daily administration. PET data at these time point are condideres sufficient to correlate plasma concentration with receptor occupancies.
The analysis performed in study 331-09-219 shows similar criticalities. The EC50 values estimated in study 331-09-219 (EC50=68, 313 and 92 ng/mL for D2, D3 and 5-HT2A receptor, respectively) would, in principle, fit better with the multiple-dose administration of brexpiprazole 4 mg/day (resulting in Css, min=112 ng/ml) rather than brexpiprazole 1 mg/day (giving Css, min=21.2 ng/ml). The Applicant was requested to provide an exposure-occupancy relationship that considers brexpiprazole trough concentrations at Day 10 pre-last dose for an adequate evaluation of receptor occupancies at the indicated time sampling. The applicant provided the trough concentrations at Day 10 pre-last dose and also figures showing the requested exposure-occupancy relationship. However, this study should not considered as informative, considering the low number of patients in each group and the consequent high CV% around PK parameters.
The off-site actions (secondary pharmacology) have primarily been investigated in the dedicated QT study. The placebo-corrected change from baseline in QTcI in study 331-10-242 showed no significant impact of brexpiprazole on cardiac repolarisation in the overall study patient population. Analysis of the placebo-corrected change from baseline in QTcI in study 331-10-242 showed no significant impact of brexpiprazole on cardiac repolarization in the overall study patient population at the recommended dose (4 mg) and supratherapeutic dose (12 mg, 3-times highest recommended dose. However, the threshold level of regulatory concern (upper bound of the 95% CI>10 ms) was observed in female patients both at therapeutic (4 mg) and supratherapeutic (12 mg) brexpiprazole doses (see also safety concerns). Further insights on these outcomes are thus deemed necessary, and the Applicant was requested toanalyze and discuss study 331-10-242 results concerning the primary endpoint (Time-matched, Placebo-adjusted Mean Change from Baseline in QTcI and QTcF) using weight categories, CYP2D6 phenotype categories (UR, EM, IM, PM) as well as concomitant medications (CYP2D6 and CYP3A4 inhibitors) and subject sex as stratification factors. The Applicant explains that any further subgroup analysis of the data (by weight or by CYP2D6 metabolic status) is not warranted due the small number of subjects expected in each category and that the range of concentrations observed in the supratherapeutic arm of study 331-10-242 are well above the slightly higher concentrations that may be observed in subjects due to weight, age, CYP2D6 metabolism status or gender.
In particular, the observed differences between genders were most likely related to the smaller number of female than male subjects in each treatment group (14 females versus 48 males for brexpiprazole 4 mg, 13 versus 40 for brexpiprazole 12 mg, and 13 versus 50 for moxifloxacin).

A supplemental exposure-response analysis in males and females were provided by the company. The model showed a non significant effect of brexpiprazole and its metabolite on QTcF in both male and female sub-groups.
The applicant has not provided any requested information on pharmacodynamic interactions of brexpiprazole. This lack of information is not deemed critical at this stage, but the prescribers must be informed of it. The following statement shoul be added to the section 4.5 of the SmPC under the subheading *"Potential for brexpiprazole to affect other medicinal products": "No information on pharmacodynamic interactions of Brexpiprazole is available at present. Caution should be exercised when prescribed with other medications."*
The applicant has stated that no genetic effects on pharmacodynamics have been investigated. The CYP2D6 genetic differences are primarily a pharmacokinetic issue. This lack of data is not deemed critical, but the prescribers should be informed of it in the product information. As requested, the following statement *"Influences of genetic variation on the pharmacodynamic responses to Brexpiprazole have not been investigated" has been added to the section 5.1 of the SmPC under the subheading "Pharmacodynamic effects".*
PK-PD relationship has been examined. Exposure-PANSS response analysis suggests that the increases of brexpiprazole dose between 1 and 4 mg were associated with PANSS improvement over placebo. No relationship between exposures was observed for increased insomnia, percent change in bodyweight or akathisia, except for a potential relationship between the 3rd tertile for Cmax and akathisia.
Overall, the pharmacodynamics of brexpiprazole has been minimally described. It is recognised that the relevance of this information is limited for the efficacy but it is more important for the safety and the posology of the product.

2.4.4. Discussion on clinical pharmacology

Clinical pharmacokinetic data have been obtained from numerous clinical pharmacology trials. Overall the clinical pharmacology of brexpiprazole and its metabolite, DM-3411 are reasonably well described characterised. Some pharmacokinetic and pharmacodynamic issues were addressed during the procedure.
The applicant has qualified brexpiprazole, DM-3411, and DM-3412, MOP-54522 OPC-54050, OPC-34835 and OPC-3952 in plasma (SFO-34318 was not quantified) following 14 days of dosing in subjects with schizophrenia (CSR 331-08-205). Furthermore, the applicant has performed sparse sampling in late phase studies and quantified brexpiprazole and DM-3411 in these studies. However, the applicant has not addressed the potential accumulation of the metabolites; while the metabolites (apart from DM-3411) appear to have minimal contribution to the primary effects of brexpiprazole, this does not negate any off-target effects if there is accumulation. In conclusion, except for DM-3411 and DM-3412 metabolites (32.6% and 5.76% of brexpiprazole exposure, respectively; SCP, the exposure to all other identified metabolites were at consistently low concentrations and no further accumulation is expected for these metabolites.
Given the lack of effect on the probes for CYP3A4, 2D6 and 2B6 enzymes following brexpiprazole dosing for 8 days, mechanism-based is unlikely.
The applicant argues that assay sensitivity decreases as the concentration of the substrate increases, which is agreed with. Nonetheless, the applicant has investigated a substrate concentration significantly lower than the concentration expected in the gut and it can be argued that it may not be physiologically relevant. Despite not being in line with recommendations in the guideline, the issue is not pursued.
The applicant has simulated the effect of coadministration of a CYP3A4 inducer on the PK of brexpiprazole, based on the clearance observed in the DDI study.

Simulations of 12 mg once daily, 16 mg once daily, 6 mg twice daily and 8 mg twice daily administration of brexpiprazole were provided by the applicant. On the basis of the submitted simulations the SmPC sections 4.2, and 4.5 have been amended to reflect that if brexpiprazole is used concomitantly with strong CYP3A4 inducers (e.g. rifampicin), the total daily dose requirement of brexpiprazole is increased by approximately a factor of three at steady state. Once daily dosing results in high peak to trough fluctuation, hence twice daily divided dosing is preferable from a PK perspective. This is reflected in the wording of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The issues raised during the procedure have been solved.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The short term efficacy of brexpiprazole for the treatment of schizophrenia was evaluated in one phase 2, three phase 3 placebo-controlled studies and one active control study:

- Trial **331-07-203** is a phase 2, 6 weeks fixed-flexible dose trial with an active reference (aripiprazole)

- Trials **331-10-231** and **331-10-230** are two phase 3, 6 weeks, fixed-dose, global trials each including a 2mg/day and a 4mg/day dose arms and a lower dose arm for each trial of 0.25mg and 1mg, respectively

- Trial **331-10-002** is a phase 3, 6 weeks fixed-dose, regional trial conducted in Japan including a 1mg/day, a 2mg/day and a 4mg/day dose arms

- Trial **14644A** is a 6 weeks, flexible-dose trial with an active reference (quetiapine) including a 2-4mg dose brexpiprazole arm

The long term efficacy of brexpiprazole for the treatment of schizophrenia was evaluated in one phase 3 long-term, maintenance trial

- Trial **331-10-232** is a multicentre double blind placebo controlled relapse prevention trial to assess the efficacy safety and tolerability of brexpiprazole (1 to 4mg/day) as maintenance treatment in adult patients with schizophrenia

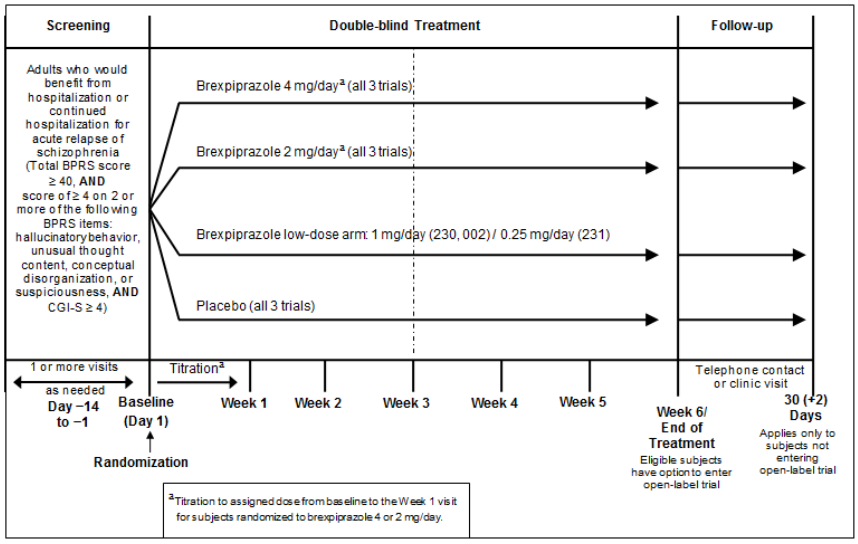
Phase 2 dose-response study 331-07-203
Trial **331-07-203** did not meet the primary or key secondary endpoints. The trial did not show assay sensitivity, as neither aripiprazole nor any of the brexpiprazole treatment arms separated from placebo. The higher numeric improvement in terms of reduction of PANSS total score, compared to placebo, was achieved with the flexible dose 0.5-1.5 mg (LS mean change -18.47) and the flexible interval 5 ± 1 (LS

mean change -18.02), although both of these differences were not statistically significant. A dose response is not clearly evident.

Table 5 Trial 331-07-203: Primary Efficacy Results (Double-blind Treatment Period) - LOCF (Efficacy Sample)

Endpoint Parameter	**Brex 0.25 mg (n=41)**	**Brex 1.0 ± 0.5 mg (n=88)**	**Brex 2.5 ± 0.5 mg (n=90)**	**Brex 5.0 ± 1.0 mg (n=92)**	**Aripiprazole 15 ± 5 mg (n=50)**	**Placebo (n=93)**
Primary Endpoint						
PANSS Total Score						
Baseline mean (SD)	97.07 (8.54)	96.33 (9.93)	98.59 (10.50)	97.76 (10.99)	97.12 (10.68)	97.62 (9.91)
LS Mean Change at Week 6	**−9.76**	**−18.47**	**−15.22**	**−17.64**	**−18.02**	**−13.77\ −14.38**
Treatment Diff[a] (95% CI)	4.62 (−2.89, 12.12)	−4.70 (−10.2, 0.82)	−1.44 (−6.96, 4.07)	−3.86 (−9.32, 1.59)	−3.64 (−10.7, 3.38)	- -
p-value[b]	**0.2263**	**0.0949**	**0.6066**	**0.1646**	**0.3074**	-

Short term studies



Study 331-10-231 results

The primary endpoint of mean change in PANSS Total Score from baseline to Week 6 was superior for the 4 mg/day (LS mean difference=−7.64, p=0.0006) and brexpiprazole 2 mg/day (LS mean difference= −8.72,
p < 0.0001) groups over placebo. The brexpiprazole 0.25 mg/day group showed practically no improvement in comparison to placebo in the change in PANSS Total Score from baseline to Week 6 (LS mean difference= −2.89, p = 0.2910). Improvement for both the 4 and the 2 mg arm was shown starting at week 2 (with some signal of efficacy already at week 1). The key secondary endpoint for this study was the LS mean change from baseline to week 6 in the CGI-S score.
The LS mean of the brexpiprazole 2mg treatment arm was -1.20 therefore the separation from placebo was statistically significant (p = 0.0056), the same applies for the 4mg treatment arm (LS mean -1.15)

which separated significantly from placebo (p = 0.0012). Patients treated with the dose of 0.25 improved minimally (LS mean change from baseline -0.85) and resulted non-statistically significant. These data provide evidence of efficacy of brexpiprazole at the dose of 2 and 4 mg/day in terms of reduction of psychotic symptoms as measured by the PANSS. No clear dose-response is observed.

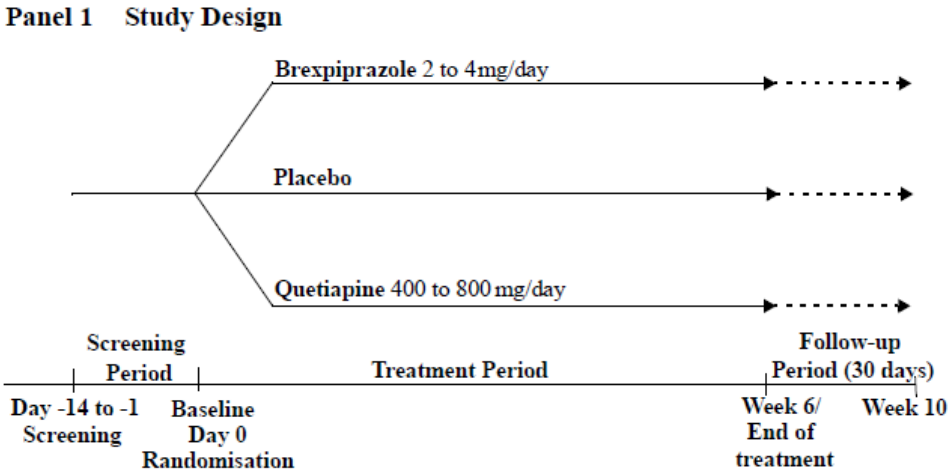
Study 331-10-230 results

The demographic characteristics were balanced across the treatment arms. Of 674 randomised patients, 657 were included in the efficacy analysis set and 32% did not complete the study.
Only patients treated with brexpiprazole 4 mg showed a statistically significant separation from placebo in the primary endpoint (change from baseline to week 6 at the PANSS) and key secondary endpoint (change from baseline to week 6 in CGI-S). Patients on placebo improved -13.53 in 6 weeks compared to patients on brexpiprazole 4mg who improved -20 points. Patients on brexpiprazole 2 mg showed a reduction of -16.6 at the PANSS and therefore their difference with placebo was not statistically significant. Patients in the brexpiprazole 1mg arm improved as much as those on 2mg (-16.9 points), although the randomization was unbalanced and the 1 mg arm counted only 117 patients. The onset of efficacy, when measured at the PANSS, was already significant at week 1, but only in the 4 mg arm. The difference in CGI-S scores between treatment and placebo showed a similar pattern where only patients in the 4 mg arm separated significantly from placebo (-1.19 LS mean vs -0.81 treatment and placebo respectively). Numeric improvement in the 2 mg and 1 mg arms was similar.These results support an effect of brexpiprazole in reducing schizophrenia symptoms as measured by the PANSS at the dose of 4 mg. In addition, the dose of 1 mg shows similar results as the dose of 2 mg.

Study 331-10-002 (Japan) results

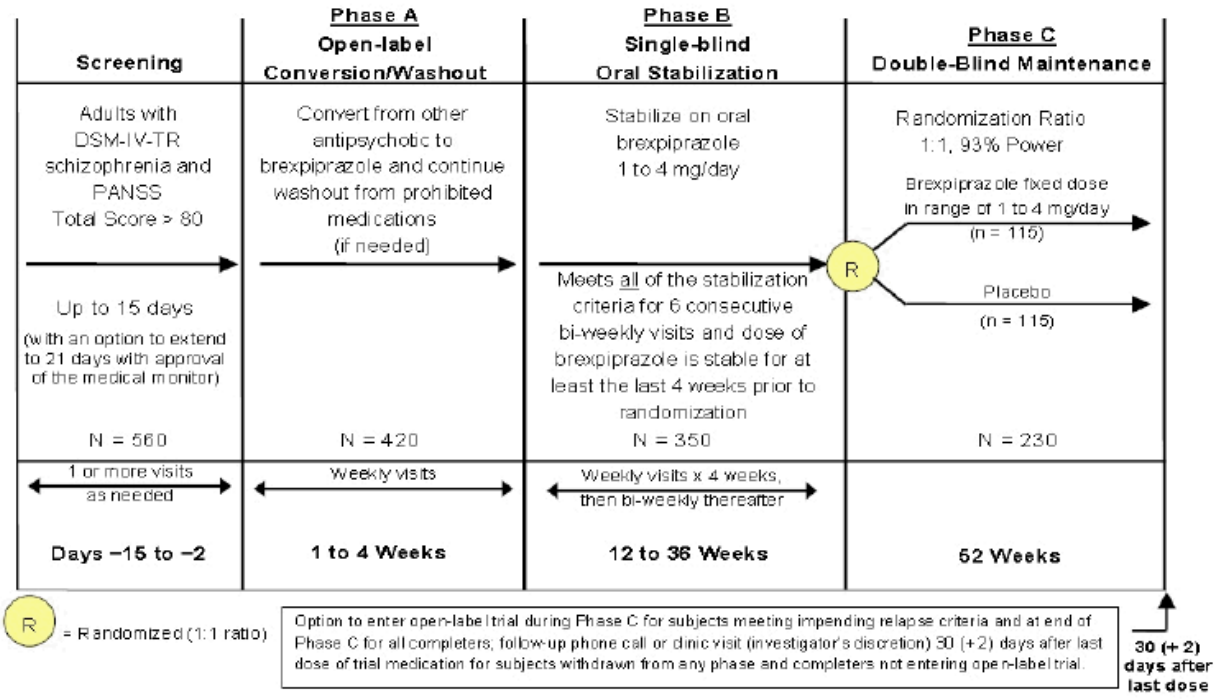
Between 40% and 30% of patients discontinued from the study depending on study arm and as expected the highest discontinuation rate was found in the placebo arm. The relative proportion of males in the study is sensibly lower as compared to studies 231 and 230. In this regional phase 3 short term pivotal study only patients treated with brexpiprazole 2 mg showed a statistically significant separation from placebo in the primary endpoint (change from baseline to week 6 at the PANSS). Of note, the placebo group improved less than in previous studies (230 & 231) with a LS mean change at week 6 of -7.63 at the PANSS. The group treated with 2 mg improved substantially (LSmean change -14.95, p = 0.0124) and kept the statistical significance also with the hochberg procedure. This difference appeared at week 3 of treatment and remained trought the study period. The group treated with 4 mg improved less (-3.86 difference from placebo, not statistically significant). The lowest numerical improvement was observed in the group treated with 1mg. These results support the efficacy of brexpiprazole in reducing schizophrenia symtoms as measured by the PANSS at the dose of 2 mg. The frequency of the CYP2D6 genotype should be taken into account when comparing these results with those from the multisite international population (studies 231, 230, and 14644A). However, the percentages of UR, EM, IM and PM are highly comparable among the three pivotal studies (331-10-002, 331-10-230 and 331-10-231), therefore it is unlikely that the inconsistency of the pivotal efficacy results with respect to brexpiprazole doses may depends on pharmacogenomic issues.

Study 14644A (short-term, flexible dose) results



In this flexible dose, active and placebo controlled study the group treated with the dose range of 2-4 mg brexpiprazole failed to separate from placebo in the difference in reduction of PANSS total scores at 6 weeks. Placebo patients showed a reduction in PANSS total scores at week 6 equal to -15,9 (higher than what seen in all the other 3 phase 3 trials), therefore the improvement with brexpiprazole (-20) was not sufficient to achieve clinical and statistical difference, whilest patients treated with flexible doses of quetiapine XR improved by -24 points therefore this different was statistically significant in comparison to placebo. The difference in CGI-S scores between the brexpiprazole group and placebo was statistcally significant (LS mean -1.2 vs -0.9 for placebo, p = 0.0142), although the numeric improvement was slightly inferior to that of the quetiapine group (LS mean -1.4, p = 0.0002). However, the primary and the key secondary endpoints had to be tested hierarchically. Therefore, since the primary endpoint was not statistically significant (p = 0.056), the analysis of the key secondary endpoint should not to be formally considered. The magnitude of treatment effect of quetiapine appears larger than brexpiprazole, and this puts the efficacy of brexpiprazole in context even though it is acknowledged that the trial is not powered for superiority or head to head comparison.

Long term relapse prevention study 331-10-232



Note: Numbers of subjects shown are planned, not actual.
Note: Subjects who did not need a washout period of other antipsychotic treatments or prohibited medications could enter the Single-blind Stabilization phase directly.

The primary efficacy endpoint in Trial 331-10-232 was the time from randomization to impending relapse. The prespecified interim analysis of efficacy data for time to impending relapse included 167 randomized subjects and 45 events (50% of projected total of 90 events). The results of the interim analysis, which was performed by an independent committee, showed that time to impending relapse was statistically significantly delayed with brexpiprazole compared with placebo ($p = 0.0008$; log-rank test). The hazard ratio from the Cox proportional hazard model for the brexpiprazole to placebo comparison was 0.338 (95% CI: 0.174, 0.655). Based on this outcome and prespecified criteria in the protocol, the independent committee recommended to terminate the trial.

The final efficacy analysis included 53 impending relapse events in 200 randomized subjects included in the efficacy sample, of whom 13.54% of brexpiprazole and 38.46% of placebo subjects met the criteria for an impending relapse. The results were consistent with the interim analysis results in showing that time to impending relapse was statistically significantly delayed with brexpiprazole compared with placebo ($p < 0.0001$; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to brexpiprazole comparison in the final analysis was 0.292 (95% CI: 0.156, 0.548); thus, subjects in the brexpiprazole group had a 71% lower risk of experiencing impending relapse than the subjects in the placebo group.

The percentage of subjects meeting the criteria for impending relapse at end of the Double-blind Maintenance phase in the interim analyses was significantly lower ($p = 0.0016$) in the brexpiprazole group (15.38%) than in the placebo group (37.08%). In the final analysis, the percentage of subjects meeting the impending relapse criteria was statistically significantly lower ($p < 0.0001$) in the brexpiprazole group (13.54%) than in the placebo group (38.46%). For both treatment groups in both the interim and final analyses, the most common criterion for impending relapse met was the CGI-I (overall improvement) + PANSS (symptom severity) scores criterion followed by hospitalization.

Only 23 subjects met the stabilization criteria at doses of 1 or 2 mg. The majority of patients (between 63% and 83%) were stable at the dose of 4 mg depending on the week of treatment.

Results of other secondary endpoints (evaluated for final analyses only) supported the efficacy of brexpiprazole 1 to 4 mg/day in the maintenance treatment of schizophrenia. These included a larger proportion of subjects meeting stability criteria, improvement in clinical symptomology (as assessed by PANSS, CGI-S, and CGI-I [ANOVA, LOCF]), improved functioning (as assessed by PSP and GAF scales [ANOVA, LOCF]), and prolonged time to trial discontinuation, as compared with placebo.
The proportion of subjects who continued to meet criteria for stability at the last visit in the Double-blind Maintenance phase was 79.17% in the brexpiprazole group compared with 56.73% in the placebo group (p = 0.0007). The mean PANSS Total Score was maintained during the Double-blind Maintenance phase in subjects randomised to brexpiprazole; whereas, mean scores worsened for subjects randomized to placebo. Comparable results were observed in mean change from baseline on the PANSS Positive and Negative Subscale scores and Marder Factor scores, PEC, CGI-S, and CGI-I scores at endpoint. The PSP and GAF scales, which assess functioning, were supportive of the efficacy of brexpiprazole treatment, as was the time to trial discontinuation (for reasons other than termination of the trial for positive interim analysis).

2.5.2. Main studies

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6 Summary of efficacy for trial 331-10-231

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Three Fixed Doses of OPC-34712 in the Treatment of Adults with Acute Schizophrenia			
Study identifier	331-10-231		
Design	Phase 3, multicenter, multinational, randomized, double-blind, fixed dose, placebo-controlled trial in adult subjects with an acute relapse of schizophrenia		
	Duration of screening: Duration of main phase: Duration of follow up:		14 days 6 weeks 30 days (or enter into the extension)
Hypothesis	Superiority of 2 and 4 mg/day of brexpiprazole to placebo		
Treatment groups (Randomization: 2:2:1:2)	Brexpiprazole		Tablet 4 mg n= 180 patients randomized Tablet 2 mg n= 182 patients randomized Tablet 0.25 mg n= 90 patients randomized
	Placebo (PBO)		Tablet 0 mg n=184 patients randomized
Endpoints and definitions	Primary endpoint	PANSS	PANSS total score change from Baseline to Week 6
	Key secondary endpoint	CGI-S	CGI-S score change from Baseline to Week 6
	Secondary endpoint	PSP	PSP score change from Baseline to Week 6
	Secondary endpoint	PANSS Pos	PANSS change from Baseline to Week 6 in positive subscale scores

	Secondary endpoint	PANSS Neg	PANSS change from Baseline to Week 6 in negative subscale scores
	Secondary endpoint	CGI-I	CGI-I score to Week 6
	Secondary endpoint	Response rate	Improvement in mean change of ≥30% from baseline in PANSS Total Score at Week 6, or CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6
	Secondary endpoint	Discontinuation rate	Discontinuation rate for lack of efficacy during the trial
	Secondary endpoint	PEC	PANSS Excited Component Score change from Baseline to Week 6
	Secondary endpoint	PANSS Marder Factor	PANSS Marder Factor scores change from Baseline to Week 6

Results and Analysis

Analysis description	**Primary Analysis**				
Descriptive statistics and estimate variability					
Analysis population and time point description	Efficacy Sample: all subjects in the Safety Sample (who were randomized to treatment and took at least 1 dose of IMP) who had baseline and at least 1 post-baseline efficacy evaluation. Pairwise comparisons of the primary endpoint for 2mg/d and 4mg/d vs placebo were performed using a stepwise testing approach to adjust for multiple comparisons at a significance level of 0.05. If the results for comparison of both groups were significant, comparison between the 0.25 mg/d group vs placebo was also performed. Analysis of mean change was performed with MMRM.				
PANSS total score change from Baseline to Week 6, MRM, Efficacy Sample	Treatment group	0.25 mg	2mg	4 mg	PBO
	Number of subject	87	180	178	178
	LS mean change	-14.90	-20.73	-19.65	-12.01
	Treatment Difference	-2.89	-8.72	-7.64	-
	95% CI	-8.27,2.49	-13.1,-4.37	-12.0,-3.30	
	p-value	**0.2910**	**<0.0001**	**0.0006**	
Analysis description	**Secondary analysis**				
Descriptive statistics and estimate variability	Efficacy Sample: all subjects in the Safety Sample (who were randomized to treatment and took at least 1 dose of IMP) who had baseline and at least 1 post-baseline efficacy evaluation.				

Statistical Methods	Pairwise comparisons of the key secondary endpoint were performed using a stepwise test procedure to adjust for multiple comparisons at a significance level of 0.05. Analysis of mean change from baseline was performed with MMRM. Analysis of dichotomous variable were analyzed using the CMH general association test controlling for trial site.				
CGI-S Score change from Baseline to Week 6, MMRM, Efficacy Sample	Treatment group	0.25 mg	2mg	4 mg	PBO
	Number of subject	89	181	178	181
	LS mean change	-0.85	-1.15	-1.20	-0.82
	Treatment Difference	-0.03	-0.033	-0.38	-
	95% CI	-0.31,0.26	-0.56,-.10	-0.61,-0.15	
	p-value	**0.8491**	**0.0056**	**0.0012**	
PSP score change from Baseline to Week 6, , MMRM, Efficacy Sample	Number of subject	86	173	168	170
	LS mean change	11.84	13.15	12.72	10.26
	Treatment Difference	1.58	2.89	2.46	-
	95% CI	-1.58,4.74	0.37,5.42	-0.06,4.98	
	p-value	0.3264	0.0250	0.0557	
PANSS PositiveSubscale score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-5.46	-6.57	-6.78	-4.35
	Treatment Difference	-1.11	-2.22	-2.44	-
	95% CI	-2.90,0.68	-3.67,-0.77	-3.88,-0.99	
	p-value	0.2227	0.0029	0.0010	
PANSS Negative Sub-Scale Score change from Baseline to Week 6, MRM, Efficacy Sample	Number of subject	87	180	178	178
	LS mean change	-3.31	-4.02	-3.65	-2.24
	Treatment Difference	-1.07	-1.78	-1.41	-
	95% CI	-2.33,0.20	-2.81,-0.76	-2.44,-0.39	
	p-value	0.0996	0.0007	0.0069	
CGI-I Score at Week6 (CMH differ test), Efficacy Sample, LOCF	Mean (SD)	3.37(1.46)	2.94(1.34)	2.94 (1.29)	3.48(1.47)
	Treatment Difference	-014	-0.54	-0.50	-
	95% CI	-0.50,0.22	-0.82,-0.26	-0.77,-0.22	
	p-value	0.4505	0.0002	0.0004	
Response Rate, CMH test, Efficacy Sample	n (%)	34 (39.08)	86 (47.78)	82 (46.07)	54(30.34
	Relative Risk	1.27	1.59	1.48	-
	p-value	0.1576	0.0004	0.0032	
Discontinuation rate, CMH test, Efficacy Sample	n (%)	7 (8.05)	17 (9.44)	7 (3.93)	18 (10.1)
	Relative Risk	0.77	0.87	0.39	
	p-value	0.5115	0.6606	0.0143	
PEC Score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-1.99	-2.87	-2.75	-1.64
	Treatment Difference	-0.34	-1.22	-1.10	-
	95% CI	-1.53,0.85	-2.19,-0.26	-2.06,-0.14	
	p-value	0.5706	0.0131	0.0246	

Notes	*Cochran-Mantel-Haenszel (CMH) row mean scores differ test controlling for site. Note: 2mg and 4mg vs placebo to be evaluated also with Hochberg procedure: both p-values<0.05 or at least one p-value<0.025 Efficacy Sample for each endpoint slightly change due to the availability of at least one post-baseline evaluation.

Table 7 Summary of efficacy for trial 331-10-230

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Fixed-dose OPC-34712(4, 2, and 1 mg/day) in the Treatment of Adults with Acute Schizophrenia			
Study identifier	331-10-230		
Design	phase 3, multicenter, multinational, randomized, double-blind, fixed dose, placebo-controlled trial in adult subjects with an acute relapse of schizophrenia		
	Duration of screening: Duration of main phase: Duration of follow up:		14 days 6 weeks 30 days (or enter into the extension)
Hypothesis	Superiority of 2 and 4 mg/day of brexpiprazole to placebo		
Treatment groups (Randomization 3:3:2:3)	Brexpiprazole		Tablet 4 mg n= 184 patients randomized Tablet 2 mg n= 186 patients randomized Tablet 1 mg n= 120 patients randomized
	Placebo (PBO)		Tablet 0 mg n=184 patients randomized
Endpoints and definitions	Primary endpoint	PANSS	PANSS total score change from Baseline to Week 6
	Key secondary endpoint	CGI-S	CGI-S score change from Baseline to Week 6
	Secondary endpoint	PSP	PSP score change from Baseline to Week 6
	Secondary endpoint	PANSS Pos	PANSS change from Baseline to Week 6 in positive subscale scores
	Secondary endpoint	PANSS Neg	PANSS change from Baseline to Week 6 in negative subscale scores
	Secondary endpoint	CGI-I	CGI-I score change from Baseline to Week 6
	Secondary endpoint	Response rate	Improvement in mean change of ≥30% from baseline in PANSS Total Score at Week 6, or CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6
	Secondary endpoint	Discontinuation rate	Discontinuation rate for lack of efficacy during the trial
	Secondary endpoint	PEC	PANSS Excited Component Score change from Baseline to Week 6
	Secondary endpoint	PANSS Marder Factor	PANSS Marder Factor scores change from Baseline to Week 6
Results and Analysis			
Analysis description	**Primary Analysis**		

Descriptive statistics and estimate variability					
Analysis population and time point description	Efficacy Sample: all subjects in the Safety Sample (who were randomized to treatment and took at least 1 dose of IMP) who had baseline and at least 1 postbaseline efficacy evaluation. Pairwise comparisons of the primary endpoint for 2mg/d and 4mg/d vs placebo were performed using a stepwise testing approach to adjust for multiple comparisons at a significance level of 0.05. If the results for comparison of both groups were significant, comparison between the 1 mg/d group vs placebo was also performed. Analysis of mean change from baseline was performed with MMRM.				
PANSS total score change from Baseline to Week 6, MMRM, Efficacy Sample	Treatment group	1 mg	2mg	4 mg	PBO
	Number of subject	117	179	181	180
	LS mean change	-16.9	-16.6	-20.0	-13.5
	Treatment Difference	-3.37	-3.08	-6.47	-
	95% CI	-8.06,1.32	-7.23,1.07	-10.6,-2.35	
	p-value	**0.1588**	**0.1448**	**0.0022**	
Analysis description	**Secondary analysis**				
Descriptive statistics and estimate variability					
Statistical Methods	Efficacy Sample Pairwise comparisons of the key secondary endpoint were performed using a stepwise test procedure to adjust for multiple comparisons. Analysis of mean change from baseline was performed with MMRM. Analysis of dichotomous variable were analyzed using the CMH general association test controlling for trial site.				
CGI-S Score change from Baseline to Week 6, MMRM, Efficacy Sample	Treatment group	1 mg	2mg	4 mg	PBO
	Number of subject	120	180	183	181
	LS mean change	-0.91	-0.99	-1.19	-0.81
	Treatment Difference	-0.10	-0.19	-0.38	-
	95% CI	-0.37,0.16	-0.42,0.05	-0.62,-0.15	
	p-value	**0.4449**	**0.1269**	**0.0015**	
PSP score change from Baseline to Week 6, MMRM, Efficacy Sample	Number of subject	105	170	174	163
	LS mean change	11.73	10.52	13.11	8.52
	Treatment Difference	3.21	2.00	4.59	-
	95% CI	0.26,6.16	-0.58,4.59	2.02,7.17	
	p-value	0.0332	0.1286	0.0005	
PANSS Positive Subscale score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-5.63	-5.42	-6.65	-4.95
	Treatment Difference	-0.68	-0.47	-1.70	-
	95% CI	2.26,0.89	-1.86,0.93	-3.08,-0.31	
	p-value	0.3938	0.5101	0.0166	

PANSS Negative Sub-Scale Score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-2.92	-2.91	-3.36	-2.14
	Treatment Difference	-0.78	-0.77	-1.22	-
	95% CI	-1.98,0.42	-1.83,0.29	-2.28,-0.17	
	p-value	0.2004	0.1547	0.0231	
CGI-I Score at Week 6, CMH row mean scores differ test*, Efficacy Sample, LOCF	Mean (SD)	3.20(1.45)	3.17(1.34)	2.95 (1.33)	3.48(1.46)
	Treatment Difference	-024	-0.30	-0.49	-
	95% CI	-0.56,0.08	-0.60,-0.01	-0.78,-0.20	
	p-value	0.1358	0.0422	0.0009	
Response Rate, CMH test, Efficacy Sample, LOCF	n (%)	51(43.59)	69 (38.55)	90 (49.72)	57(31.7)
	Relative Risk	1.35	1.22	1.54	-
	p-value	0.0433	0.1680	0.0006	
Discontinuation rate, CMH test, Efficacy Sample	n (%)	9 (7.69)	20 (11.17)	16 (8.84)	21(11. 7)
	Relative Risk	0.76	1.00	0.82	
	p-value	0.4586	0.9894	0.5202	
PEC Score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-1.94	-1.90	-2.86	-1.47
	Treatment Difference	-0.48	-0.43	-1.39	-
	95% CI	-1.51,0.56	-1.34,0.48	-2.30,-0.48	
	p-value	0.3646	0.3559	0.0029	
Notes	*Cochran-Mantel-Haenszel (CMH) row mean scores differ test controlling for site. Note: 2mg and 4mg vs placebo to be evaluated also with Hochberg procedure: both p-values<0.05 or at least one p-value<0.025 Efficacy Sample for each endpoint slightly change due to the availability of at least one post-baseline evaluation.				

Table 8 Summary of efficacy for trial 331-10-002

Title: A Phase 3, Regional (Japan), Randomized, Double-blind, Placebo-controlled Trial of Fixed-dose OPC-34712(4, 2, and 1 mg/day) in the Treatment of Adults with Acute Schizophrenia			
Study identifier	331-10-002		
Design	phase 3, multicenter, randomized, double-blind, fixed dose, placebo-controlled trial in adult subjects with an acute relapse of schizophrenia		
	Duration of screening: Duration of main phase: Duration of follow up:		14 days 6 weeks 30 days (or enter into the extension)
Hypothesis	Superiority of brexpiprazole 2 and 4 mg/day to placebo		
Treatment groups (Randomization 1:1:1:1)	Brexpiprazole		Tablet 4 mg n= 113 patients randomized Tablet 2 mg n= 115 patients randomized Tablet 1 mg n= 115 patients randomized
	Placebo (PBO)		Tablet 0 mg n=116 patients randomized
Endpoints and definitions	Primary endpoint	PANSS	PANSS total score change from Baseline to Week 6
	Secondary endpoint	CGI-S	CGI-S score change from Baseline to Week 6
	Secondary endpoint	PANSS Pos	PANSS change from Baseline to Week 6 in positive subscale scores

	Secondary endpoint	PANSS Neg	PANSS change from Baseline to Week 6 in negative subscale scores
	Secondary endpoint	CGI-I	CGI-I score change from Baseline to Week 6
	Secondary endpoint	Response rate	Improvement in mean change of ≥30% from baseline in PANSS Total Score at Week 6, or CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6
	Secondary endpoint	Discontinuation rate	Discontinuation rate for lack of efficacy during the trial
	Secondary endpoint	PEC	PANSS Excited Component Score change from Baseline to Week 6
	Secondary endpoint	PANSS Marder Factor	PANSS Marder Factor scores change from Baseline to Week 6

Results and Analysis

Analysis description	**Primary Analysis**				
Descriptive statistics and estimate variability					
Analysis population and time point description	Efficacy Sample: all subjects in the Safety Sample (who were randomized to treatment and took at least 1 dose of IMP) who had baseline and at least 1 postbaseline efficacy evaluation. Pairwise comparisons of the primary endpoint for 2mg/d and 4mg/d vs placebo were performed using a stepwise testing approach to adjust for multiple comparisons at a significance level of 0.05. If the results for comparison of both groups were significant, comparison between the 1 mg group vs placebo was also performed. Analysis of mean change from baseline was performed with MMRM.				
PANSS total score change from Baseline to Week 6, MMRM, Efficacy Sample	Treatment group	1 mg	2mg	4 mg	PBO
	Number of subject	112	113	109	113
	LS mean change	-8.26	-14.95	-11.49	-7.63
	Treatment Difference	-0.63	-7.32	-3.86	-
	95% CI	-6.50, 5.24	-13.04,-1.59	-9.71, 2.00	
	p-value	**0.8330**	**0.0124**	**0.1959**	
Analysis description	**Secondary analysis**				
Descriptive statistics and estimate variability					
Statistical Methods	Efficacy Sample Analysis of mean change from baseline was performed with MMRM. Analysis of dichotomous variable were analyzed using the CMH general association test controlling for trial site.				

CGI-S Score change from Baseline to Week 6, MMRM, Efficacy Sample	Treatment group	1 mg	2mg	4 mg	PBO
	Number of subject	112	113	109	113
	LS mean change	-0.52	-0.85	-0.62	-0.57
	Treatment Difference	-0.04	-0.28	-0.05	-
	95% CI	-0.27,0.36	-0.58, 0.03	-0.37, 0.26	
	p-value	0.7770	0.0727	0.7316	
PANSS Positive Subscale score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-2.22	-4.32	-3.15	-3.69
	Treatment Difference	1.47	-0.62	0.54	-
	95% CI	-0.31, 3.26	-2.37, 1.12	- 1.24,2.32	
	p-value	0.1047	0.4814	0.5506	
PANSS Negative Sub-Scale Score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-2.34	-3.48	-3.24	-1.20
	Treatment Difference	-1.14	-2.28	-2.04	-
	95% CI	-2.67, 0.39	-3.77,-0.79	-3.57,-0.52	
	p-value	0.1426	0.0028	0.0087	
CGI-I Score at Week 6, CMH row mean scores differ test*, Efficacy Sample, LOCF	Mean (SD)	3.90(1.32)	3.49(1.30)	3.78 (1.33)	3.83(1.49)
	Treatment Difference	0.07	-0.35	-0.05	-
	95% CI	-0.30, 0.44	-0.71, 0.02	-0.43, 0.32	
	p-value	0.8003	0.0884	0.7891	
Response Rate, CMH test, Efficacy Sample, LOCF	n (%)	18 (16.07)	99 (25.66)	27 (24.77)	23(20.35
	Treatment difference	-4.28	5.31	4.42	-
	p-value	0.4054	0.3430	0.4310	
Discontinuation rate, CMH test, Efficacy Sample	n (%)	7(6.25)	9 (7.96)	9 (8.26)	7(6.19)
	Treatment difference	0.06	1.77	2.06	-
	p-value	0.9863	0.6040	0.5525	
PEC Score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-0.72	-2.08	-1.58	-1.14
	Treatment Difference	-0.42	-0.94	-0.44	-
	95% CI	-0.71, 1.55	-2.05, 0.16	-1.58, 0.69	
	p-value	0.4664	0.0946	0.4432	
Notes	*Cochran-Mantel-Haenszel (CMH) row mean scores differ test controlling for site. Note: 2mg and 4mg vs placebo to be evaluated also with Hochberg procedure: both p-values<0.05 or at least one p-value<0.025 Efficacy Sample for each endpoint slightly change due to the availability of at least one post-baseline evaluation.				

Table 9 Summary of efficacy for trial 14644A

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled and active reference Trial of Flexible-dose OPC-34712 (2-4 mg/day) in the Treatment of Adults with Acute Schizophrenia	
Study identifier	14644A
Design	phase 3, multicenter, randomized, double-blind, flexible dose, placebo-controlled and active reference trial in adult subjects with an acute relapse of schizophrenia

	Duration of screening: Duration of main phase: Duration of follow up:	14 days 6 weeks 30 days (or enter into the extension)		
Hypothesis	Superiority to placebo of dose range 2 -4 mg/day			
Treatment (Randomization 1:1:1)	Brexpiprazole		2-4mg/day n=151 randomized	
	Quetiapine		400-800mg/day n=154 randomized	
	Placebo		Placebo, n=163 randomized	
Endpoints and definitions	Primary endpoint	PANSS	PANSS total score change from Baseline to Week 6	
	Key Secondary endpoint	CGI-S	CGI-S score change from Baseline to Week 6	
	Secondary endpoint	PANSS Pos	PANSS change from Baseline to Week 6 in positive subscale scores	
	Secondary endpoint	PANSS Neg	PANSS change from Baseline to Week 6 in negative subscale scores	
	Secondary endpoint	CGI-I	CGI-I score change from Baseline to Week 6	
	Secondary endpoint	Response rate	Improvement in mean change of ≥30% from baseline in PANSS Total Score at Week 6, or CGI-I score of 1 (very much improved) or 2 (much improved) at Week 6	
	Secondary endpoint	Discontinuation rate	Discontinuation rate for lack of efficacy during the trial	
	Secondary endpoint	PEC	PANSS Excited Component Score change from Baseline to Week 6	
	Secondary endpoint	PANSS Marder Factor	PANSS Marder Factor scores change from Baseline to Week 6	
Results and Analysis				
Analysis description	**Primary Analysis**			
Descriptive statistics and estimate variability				
Analysis population and time point description	Efficacy Sample: all subjects in the Safety Sample (who were randomized to treatment and took at least 1 dose of IMP) who had baseline and at least 1 postbaseline efficacy evaluation. Pairwise comparisons of the primary endpoint for 2mg/d and 4mg/d vs placebo were performed using a stepwise testing approach to adjust for multiple comparisons at a significance level of 0.05. If the results for comparison of both groups were significant, comparison between the 1 mg group vs placebo was also performed. Analysis of mean change from baseline was performed with MMRM.			
PANSS total score change from Baseline	Treatment group	Brex 2-4 mg	Que 400-800mg	PBO
	Number of subject	150	150	159

to Week 6, MMRM, Efficacy Sample	LS mean change	-20.0	-24.0	-15.9
	Treatment Difference	-4.1	-8.0	-
	95% CI	-8.2, 0.1	-12.2,-3.9	
	p-value	**0.056**	**0.0002**	
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability				
Statistical Methods	Efficacy Sample Analysis of mean change from baseline was performed with MMRM. Analysis of dichotomous variable were analyzed using the CMH general association test controlling for trial site. The overall significance level was 0.05. The primary and the key secondary endpoints (CGI-S) were tested hierarchically therefore, as the primary hypothesis could not be rejected, no further confirmatory test should be considered.			
CGI-S Score change from Baseline to Week 6, MMRM, Efficacy Sample	Treatment group	Brex 2-4 mg	Que 400-800mg	PBO
	Number of subject	150	150	159
	LS mean change	-1.2	-1.4	-0.9
	Treatment Difference	-0.3	-0.4	-
	95% CI	-0.5, -0.1	-0.6, -0.2	
	p-value	0.0142	0.0002	
PANSS Positive Subscale score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-7	-8.1	-5.4
	Treatment Difference	-1.6	-2.7	-
	95% CI	-2.9, -0.3	-4.0, -1.3	
	p-value	0.0182	<0.001	
PANSS Negative Sub-Scale Score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-3.7	-4.5	-3.1
	Treatment Difference	-0.6	-1.4	-
	95% CI	-1.7, 0.4	-2.5,-0.4	
	p-value	0.249	0.0083	
CGI-I Score at Week 6, Efficacy Sample, MMRM	Mean	2.7	2.5	3.0
	Treatment Difference	-0.3	-0.6	-
	95% CI	-0.6, 0.0	-0.8, -0.3	
	p-value	0.295	<0.0001	
Response Rate, logistic	n (%)	73(48.7)	94 (62.7)	51(32.1)
	Adjusted Odds Ratio	2.00	3.56	-

regression, Efficacy Sample, last assessment	p-value	0.0032	<0.0001	
Discontinuation rate, CMH test, Efficacy Sample	n (%)	10(6.67)	11 (7.19)	24(14.91)
	Hazard Ratio	0.44	0.45	-
	p-value	0.027	0.0269	
PEC Score change from Baseline to Week 6, MMRM, Efficacy Sample	LS mean change	-3.3	-3.9	-2.5
	Treatment Difference	-0.8	-1.3	-
	95% CI	-1.8, 0.1	-2.3, -0.4	
	p-value	0.0845	0.0043	
Notes	*Cochran-Mantel-Haenszel (CMH) row mean scores differ test controlling for site. Note: 2mg and 4mg vs placebo to be evaluated also with Hochberg procedure: both p-values<0.05 or at least one p-value<0.025 Efficacy Sample for each endpoint slightly change due to the availability of at least one post-baseline evaluation.			

Table 10 Summary of efficacy for trial 331-10-232

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) as Maintenance Treatment in Adults with Schizophrenia		
Study identifier	331-10-232	
Design	This was a phase 3 multicenter, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of brexpiprazole as maintenance treatment in adults with schizophrenia. The trial consisted of a screening period during which eligibility criteria were assessed; a period for conversion from other antipsychotic(s) to oral brexpiprazole and washout of prohibited concomitant medications, if applicable; a single-blind treatment phase to stabilize subjects on oral brexpiprazole; a double-blind randomization phase to assess maintenance of effect, and a post-treatment follow-up for safety monitoring.	
	Duration of screening phase: Duration of open-label conversion phase: Duration of open-label stabilisation phase: Duration of double-blind phase: Duration of safety follow-up phase:	up to 15 days 1-4 weeks 12 weeks Up to 52 weeks 30 days
Hypothesis	Superiority to placebo in maintenance of efficacy	
	brexpiprazole 1-4 mg	Oral tablets 78 randomized patients
	placebo	Oral tablets 89 randomized patients
Endpoints and definitions	Primary endpoint	time to impending relapse (brexpiprazole 1-4 mg group vs. placebo)
	Key secondary endpoint	Percentage of subjects meeting the impending relapse criteria

Results and Analysis

Analysis description	**Interim Analysis**		
Analysis population and time point description	Analysis of Time to Impending Relapse (Double-blind Maintenance Phase Efficacy Sample)		
Statistical Methods	This is a group sequential trial reporting the results from the 1st interim analysis. The two-sided alpha level (0.003051) was defined by the O'Brian-Fleming spending function. An additional "final" analysis was performed including 8 impending relapse events occurred between the interim analysis cu-off date and the trial termination (last visit in the Double-blind Maintenance phase).		
Time to relapse (Kaplan-Meier, Cox proportional hazards model, p-value from log-rank test)	Treatment group	placebo	brexpiprazole 1-4 mg
	Number of subjects	89	78
	Number of impending relapses (%)	33 (37.08%)	12 (15.38%)

	Hazard Ratio	-	0.338
	95 % CI	-	(0.174, 0.655)
	days to relapse, median	85	132
	P value	0.0008	
Analysis description	**Final Analysis**		
Time to relapse (Kaplan-Meier, Cox proportional hazards model, p-value from log-rank test)	Treatment group	placebo	brexpiprazole 1-4 mg
	Number of subjects	104	96
	Number of impending relapses (%)	40 (38.46%)	13 (13.54%)
	Hazard Ratio		0.292
	95 % CI		(0.156, 0.548)
	days to relapse, median	111	169
	P value	<0.0001	
Percentage of subjects meeting the impending relapse criteria (chi-square test)	Treatment group	placebo	brexpiprazole 1-4 mg
	Number of subjects	104	96
	At least one of the criteria n (%)	40(38.46)	13 (13.54)
	P value	<0.0001	

Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy of brexpiprazole 2 and 4 mg was analysed across trials in a series of pool analyses which confirmed that PANSS change from baseline to week 6 was significantly different from placebo either when the dose of 2 mg and 4 mg were analysed in separate pools and also when the doses were pooled together. As stated earlier in the assessment, this difference confirms superiority of numerical improvement at the PANSS in the brexpiprazole group as compared to placebo but does not show a clear dose-response.

If only the two global fixed dose trials are pooled, the dose response appears more pronounced (treatment effect −5.46 for 2 mg/day and −6.69 for 4 mg/day).

A flatter dose response arises when pooling also regional trial 002; which may depend on differences in the gender and mean age distribution as compared to the global trials. For this reason the Applicant provided a post hoc analysis adding age and gender as fixed effects in the MMRM model.

In study 002, brexpiprazole 4 mg/day separates from placebo ($p < 0.05$) at Week 3 (−5.05, $p = 0.0337$), Week 4 (−7.18, $p = 0.0082$), and Week 5 (−6.07, $p = 0.0420$). At Week 6, a trend towards statistical separation is observed (−5.59, $p = 0.0710$).

Analyses by Region

The Applicant presents subgroup analyses by Region, including Europe. In the single trials analyses (primary endpoint), the following observations are made in relation to the European population:
In trial 231, efficacy of both the 4 and the 2 mg dose is confirmed, with the 2 mg dose showing higher numerical improvement.
In trial 230, efficacy of the 4 mg dose is confirmed only in the North American population but not in the EU population.
In trial 14644A, despite the failure of brexpiprazole to demonstrate superiority to placebo, the numerical improvement in the EU population is superior to the numerical improvement in the North American population.
Only 218 individuals (12.1%) of those included in the efficacy population are European. All EU patients are of white ethnic background, as compared to the ROW population which had different ethnic background. The proportion of males recruited in the EU population is smaller than the ROW population. Gender distribution and ethnicity are not thought to affect B/R in the small EU population of the program.

Analyses by Age

All short term trials enrolled subjects with an age included between 18 and 65 years. In all single trials sub-group analyses, a significantly lower proportion of subjects with more than 55 years of age were enrolled. Across the 4 short term trials, 12.3% were older than 55 years of age. From the data presented by the Applicant and considering the small sample, no interaction for age was found and data do not allow to assume a different B/R in the subgroup older than 55 years.

Clinical studies in special populations

No efficacy studies have been conducted in elderly populations. Instead the applicant has submitted a subgroup analysis of change in PANSS total score by age for the 4 of the 6 efficacy studies (331-10-231, 331-10-230, 331-10-002 and 14644A). Special populations have been looked into during the development programme primarily in terms of safety but not in terms of efficacy. A paediatric investigation plan (PIP) has been agreed and its completion has been deferred to 2022. Study 331-10-233 in adolescents is marked as ongoing and a synoptic report has been submitted. The current indication restricts the use of the product to adults and no paediatric data are available yet. The lack of specific efficacy data in the elderly is reported in the SmPC.

Supportive studies

No studies have been presented as supportive.
In addition to the controlled trials the applicant has conducted following open label trials in patients with schizophrenia.

Table 11 Open label brexpiprazole clinical studies in patients with schizophrenia.

Type of Trial (Trial Phase)	Protocol Number Location of Trial	Trial Report Location	Trial Objective(s)	Trial Design and Type of Control	Investigational Medicinal Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Subjects	Treatment Duration	Trial Status; Type of Report
Efficacy, safety (Phase 3b)	331-13-008 United States	Section 5.3.5.2 [Report body] [Synopsis]	Efficacy, cognitive functioning, and safety of flexibly-dosed brexpiprazole monotherapy in subjects with acute schizophrenia	Exploratory, open-label Positive control (aripiprazole) used to benchmark the observed effects.	Brexpiprazole: Initial dose: 1 mg/day Dose range: 1 to 4 mg/day Aripiprazole: Initial dose: 10 mg/day Dose range: 10 to 20 mg/day	Enrolled: 97 Brexpiprazole: 64 Aripiprazole: 33	Subjects with acute schizophrenia	6 weeks	Complete; Report body and synopsis
Exploratory efficacy, safety (Phase 3b)	331-13-006 United States	Section 5.3.5.2 [Report body] [Synopsis]	Efficacy and safety of flexibly-dosed brexpiprazole monotherapy in subjects with early-episode schizophrenia (defined as episodes occurring ≤5 years after the start of their first schizophrenic episode)	Exploratory, open-label	Brexpiprazole tablets PO QD (1, 2, 3, or 4-mg) Conversion Period (2, 3, or 4 weeks): Brexpiprazole flexible doses of 1, 2, 3 (target dose) or 4 mg/day concurrent with decreasing doses of previous antipsychotic(s) Monotherapy Treatment Period (12 to 14 weeks, depending on duration of conversion period): Brexpiprazole flexible doses of 1, 2, 3 (target dose) or 4 mg/day	Enrolled: 49	Subjects with early episode schizophrenia	16 weeks	Complete; Report body and synopsis
Safety, tolerability, efficacy (Phase 3)	331-10-237 Multinational (North America, Europe, Asia, and Latin America)	Section 5.3.5.2 [Report body] [Synopsis]	Long-term safety, tolerability, and efficacy of brexpiprazole as monotherapy in adults with schizophrenia	Open-label trial for subjects who completed double-blind Trial 331-10-230, 331-10-231, or 331-10-232; eligible withdrawals from Phase C (maintenance) of Trial 331-10-232; and eligible "de novo" subjects Phase A: Open-label conversion to oral brexpiprazole for subjects receiving other antipsychotics at screening Phase B: Open-label brexpiprazole monotherapy	Brexpiprazole tablets PO QD: 1, 2, 3, and 4-mg Phase A (if needed): Starting dose of 1 mg/day to convert from other antipsychotic(s) to brexpiprazole monotherapy at 2 mg/day Phase B (all subjects): Starting dose of 2 mg/day; dose adjustments permitted as needed for efficacy/tolerability within range of 1 to 4 mg/day	Overall: 1072 De novo: 257 331-10-230: 287 331-10-231: 285 331-10-232: 243 Phase A[c]: 238 De novo: 226 331-10-232: 12 Phase B[c]: 1031 (Brexpiprazole monotherapy - includes subjects who converted from other antipsychotics in Phase A and those who entered the trial in Phase B) De novo: 224 331-10-230: 286 331-10-231: 278 331-10-232: 243	Subjects with schizophrenia	Up to 52 weeks[d]	Complete; Report body and synopsis
Safety, tolerability (Phase 3)	14644B Multinational (North America and Europe)	Section 5.3.5.2 [Report body] [Synopsis]	Long-term safety, tolerability, therapeutic effect, and effect on resource utilization of flexible doses of brexpiprazole in subjects with schizophrenia	Open-label extension for subjects who completed double-blind lead-in Trial 14644A	Brexpiprazole tablets PO QD: 1, 2, 3, or 4 mg Starting dose of 2 mg/day may increase to 3 mg/day at Day 8 and 4 mg/day at Day 15, or can be decreased to 1 mg/day for tolerability	Enrolled: 210	Subjects with schizophrenia	52 weeks	Complete; Report body and synopsis

Type of Trial (Trial Phase)	Protocol Number Location of Trial	Trial Report Location	Trial Objective(s)	Trial Design and Type of Control	Investigational Medicinal Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled	Healthy Subjects or Diagnosis of Subjects	Treatment Duration	Trial Status; Type of Report
Safety, tolerability, efficacy (Phase 2)	331-08-210 Multinational (North America, Europe, and Asia)	Section 5.3.5.2 [Report body] [Synopsis]	Long-term safety, tolerability, and efficacy of brexpiprazole monotherapy	Open-label trial for subjects who completed Trial 331-07-203	Brexpiprazole tablet PO QD Starting dose 2 mg/day; dose adjustments permitted as needed for efficacy/tolerability within range of 1 to 6 mg/day	Enrolled: 244 By treatment duration: 52 weeks: 28 6 weeks: 216	Subjects with schizophrenia	52 weeks for subjects enrolled after Amendment 2 6 weeks for subjects who completed Trial 331-07-203 before Amendment 2 of Trial 331-08-210	Complete; Report body and synopsis
Safety, efficacy (Phase 3)	331-10-003 Japan	Section 5.3.5.2 [Report body] [Synopsis]	Safety and efficacy of long-term brexpiprazole monotherapy in adults with schizophrenia	Open-label Period 1 (new [ie, de novo] subjects only): Open-label conversion to oral brexpiprazole for subjects receiving other antipsychotics at screening Period 2: Open-label brexpiprazole monotherapy	Period 1 (medication switching period, new subjects only): Brexpiprazole tablet (1 to 2 mg/day) + antipsychotics Antipsychotics discontinued by Week 4 of Period 1. Period 2 (treatment period): Initial dose: 2 mg/day Dose range: 1 to 4 mg/day The dose will be increased at each scheduled visit based on the specified dose-escalation criteria.	Period 1 Enrolled: 208 Period 2 Enrolled: 282	Subjects with schizophrenia	52 weeks	Complete; Report body and synopsis

Some of the studies listed as the main have more supportive than pivotal role in the development programme. All studies listed in support of the claim of efficacy have been presented and assessed under the Main Studies heading above.
The applicant has not made any claims regarding efficacy based on the open label studies.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies
Efficacy of brexpiprazole was studied in three 6 weeks, fixed-dose, placebo-controlled pivotal trials (331-10-**231** and 331-10-**230)**, one of which is a regional study conducted in Japan (331-10-**002**). In addition, another pivotal study was a six-weeks, flexible-dose study with active reference quetiapine (**14644A**). A relapse prevention study with a randomized withdrawal phase was conducted to assess long-term maintenance efficacy of brexpiprazole in schizophrenia (331-10-**232**).
A 6-weeks dose-finding study with active reference aripiprazole was also conducted (**203**). The doses of brexpiprazole utilized in the phase 3 program ranged between 0.25 mg/day and 4 mg/day and were selected based on the collective efficacy, safety, and D2 occupancy data from a positron emission tomography (PET) trial in healthy subjects (Trial **331-07-202**) and a phase 2 trial in adults with an acute relapse of schizophrenia (Trial **331-07-203**). The results from the PET trial, predicted steady-state D2 receptor occupancies of 79.3% at brexpiprazole 1 mg/day, 88.8% at brexpiprazole 2 mg/day, and 95.1% at brexpiprazole 4 mg/day. For a D2 partial agonist, ≥ 85% receptor occupancy is generally considered to be the threshold for a clinical effect versus a 65% to 80% threshold for D2 antagonists.

In addition, the applicant conducted four pivotal studies out of which three were placebo-controlled despite the EMA Guidelines for the investigation of products for schizophrenia recommended a three-arm study of placebo, test product and active comparator. The lack of an active comparator arm in studies 331-10-231, 331-10-230 and 331-10-002 is a limitation for the efficacy assessment.
The study 14644A is a flexible dose double blind placebo and active control study; this design is more informative, the active comparator is quetiapine, however, the most suitable comparator should have been aripiprazole. The Applicant states that the active reference was added only to confirm assay sensitivity and no comparison between brexpiprazole and quetiapine has been carried out.
Each of the three fixed-dose trials investigated the efficacy and safety of the dose of 2mg/day and 4mg/day, but also had a lower dose arm. With the exception of the 331-10-002 regional study, the randomization was imbalanced with fewer patients in the lower doses arms. In the 231 study the lower dose was 0.25mg (3:3:2:3 randomization), in the 230 study the lower dose was 1mg (2:2:1:2 randomization) and in the 002 trial the lower dose was 1mg (1:1:1:1 randomization).
The choice to investigate lower doses is appreciated because the minimum effective dose should be established. Indeed, from the PET studies it appears that brexpiprazole possesses a pharmacologic activity compatible with producing clinical effects already at the dose of 1mg. The titration scheme differs between the fixed dose trials (maximum dose of 4 mg is reached in 7 days) and the flexible dose trial (maximum dose of 4mg/day is reached in 4 days). In the latter, the titration scheme is faster to allow a comparison with the established quetiapine titration scheme.
The fact that evidence of efficacy comes solely from the three fixed dose trials, implies that the maximum dose of 4mg/day should be reached through Day7, so modification to the SmPC recommendations were propsed and accepted by the Applicant
All 4 short term trials have the same primary endpoint which is "change from baseline to week 6 in the PANSS total score". The PANSS is an established and clinically meaningful endpoint and the choice of the same primary outcome measure for all trials allows comparability. As per Guidelines the CGI-S scale was chosen as a key secondary endpoint to allow assessment of clinical meaningfulness.
The primary efficacy analysis, most of sensitivity analyses and secondary efficacy analyses, are comparable across trials. The MMRM with a MAR assumption was chosen as primary efficacy analysis.
The protocol-specified primary efficacy endpoint for the fixed-dose, short-term trials (331-10-231, 331-10-230, and 331-10-002) was the change from baseline to Week 6 in PANSS Total Score.
The PANSS Total Score was evaluated with assumption of missing data being missing at random (MAR) using mixed model repeated measures (MMRM) analysis. The MMRM model with fixed-effect factors of trial site (global Trials 331-10-231 and 331-10-230 only), treatment, visit, treatment-visit interaction, and fixed-effect covariates of baseline and baseline-visit interaction was applied to the change from baseline from Week 1 to Week 6 based on all available data (observed cases [OC]).
The data were modelled using an unstructured variance-covariance matrix for the within-subject variation. The statistical test of the least squares mean differences (LSMDs) between brexpiprazole at 4 mg/day and 2 mg/day doses and placebo at Week 6 of the MMRM analysis served as the analysis of the primary efficacy endpoint. For the regional Trial 331-10-002, the MMRM model applied to the protocol-specified analysis did not include trial site as a factor; however, trial site was included in the comparison across trials.
For Trial 14644A, the primary endpoint was analysed using the same MMRM model as for the fixed-dose Trials 331-10-231 and 331-10-230 with trial site, visit, and treatment as fixed effects, baseline score as a continuous covariate, treatment-by-visit interaction, and baseline score-by-visit interaction. An unstructured covariance structure was used to model the within-subject errors. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. The analysis was based on all available observations in the treatment period (from baseline to the completion/withdrawal visit) from the brexpiprazole, quetiapine, and the placebo treatment groups. The mean differences between

brexpiprazole 2 to 4 mg/day and placebo were estimated based on least squares (LS) means in the MMRM model.
The primary statistical comparisons of interest for all efficacy analyses in the fixed-dose trials were brexpiprazole 4 mg/day versus (vs) placebo and brexpiprazole 2 mg/day vs placebo. In the flexible-dose Trial 14644A, the primary statistical comparison of interest for all efficacy analyses was the difference between brexpiprazole 2 to 4 mg/day and placebo at Week 6. Although not part of the primary analysis, quetiapine vs placebo was analyzed for assay sensitivity using the same method described for the comparison of brexpiprazole 2 to 4 mg/day vs placebo, which included all available observations in the treatment period from the brexpiprazole, quetiapine, and placebo groups.
The Hochberg procedure was specified in the original protocols to control for multiplicity in the analysis of the primary endpoint and key secondary endpoints in Trials 231 and 230 and in the analysis of the primary endpoint in Trial 002. The Hochberg procedure was replaced by the Average Effect method (stepwise procedure) to handle multiplicity in the analysis in Amendment 2 to protocols 231 and 230 and Amendment 6 of protocol 002 while the trials were still blinded.
Sensitivity analyses were performed to assess the robustness of trial results, since they are based on the MAR assumption. In the phase 3 short-term, placebo-controlled trials, sensitivity analyses for the MAR assumption were performed under various assumptions of selected data being missing not at random (MNAR). These analyses used Pattern Mixture Models based on multiple imputation (MI) with mixed missing data mechanisms. Analysis of covariance (ANCOVA) on the last observation carried forward (LOCF) dataset was also performed in these trials to allow for comparison with legacy trials.
Other secondary endpoints are: PANSS positive subscale, PANSS negative subscale, PANSS Marder Factor, the CGI-I and the PSC functional scale. In addition proportion of responders and proportion of withdrawals due to lack of efficacy are included in the evaluation. All clinical continuous endpoints assessing the antipsychotic effect of brexpiprazole are based on the PANSS. Ideally primary and secondary endpoints should measure different concepts of interest so that they provide complementary and contextual information, rather than redundant information.
The definition of response provided in the protocol uses either of the following criteria: ≥30% PANSS reduction OR CGI-I score of 1 (very much improved) or 2 (much improved). The Applicant provided also a sensitivity analysis with the proportion of responders who achieved a 40% or 50% reduction from baseline.
The maintenance study is a relapse prevention study with a double blind randomized withdrawal phase where patients are randomized to flexible doses of brexpiprazole (1-4mg) and placebo after a 12 weeks stabilization phase.
In this type of study the definition of impending relapse is of pivotal importance. The Applicant discussed the proposed definition and it was concluded that the definition of impending relapse (and not full relapse) was confirmed/reviewed by a Relapse Adjudication Committee and the definition is consistent with that of previous registrational trials (aripiprazole) and scientific literature. It is acknowledged that impending relapse, as opposed to relapse, is an endpoint that assures the safety of the subjects in the trial.

Dose finding
Study 331-07-203 is a dose finding study where doses from 0.25 up to 6 mg are tested. Aripiprazole flexible doses from 10 to 20 mg were used for assay sensitivity. The size of the samples for each dose arm are compatible with a phase 2 setting.
Patients were selected with similar criteria as compared to the phase 3 studies.
The primary efficacy endpoint (change from baseline in the PANSS Total score at week 6) was analyzed using ANCOVA in the LOCF dataset. This method is less conservative than the MMRM in this context, however results were confirmed also with the MMRM (efficacy sample).

This study could be regarded negative for both efficacy (superiority to placebo) and assay sensitivity: neither brexpiprazole, nor aripiprazole separated from placebo. This could be due to a greater than expected improvement in the placebo arm (LS mean change -13.77/-14.38, however this is only speculative. The higher numeric improvement in terms of reduction of PANSS total score, compared to placebo, was achieved with the flexible dose 0.5-1.5 mg (LS mean change -18.47) and the flexible interval 5±1 (LS mean change-18.02), although this was not statistically significant.
The lower 0.25 dose and the flexible 2-3 mg dose groups showed a lower numerical improvement (LS mean change -9.76 and -15.22, respectively).
A dose response is not clearly evident, which suggests a non-linear receptor occupancy between 1 and 6 mg, which however is not confirmed in the PET study 331-09-219 at steady state (in patients) where relevant D2/D3 occupancy was observed.

Efficacy data and additional analyses
The first pivotal phase 3 study (331-10-**231**) supports efficacy of brexpiprazole at the doses of 2 and 4 mg/day in terms of reduction of symptoms as measured by the PANSS.
The mean reduction of PANSS total score at week 6 was -20.73 for the group treated with 2mg and was -19.65 for the group treated with 4mg, therefore the separation from placebo (LS mean -12) was statistically significant ($p < 0.0001$ and $p = 0.0006$, respectively). Patients treated with the dose of 0.25 improved minimally (LS mean change from baseline -14.90), although the power calculated for the 0.25 arm was less than 70% (imbalanced randomization).
Efficacy is also supported by the results at the key secondary endpoint change from baseline to week 6 in the CGI-S score. The LS mean of the brexpiprazole 2mg treatment arm was -1.20 therefore the separation from placebo was statistically significant ($P = 0.0056$), the same applies for the 4mg treatment arm (LS mean -1.15), which separated significantly from placebo ($p = 0.0012$). Patients treated with the dose of 0.25 improved minimally (LS mean change from baseline -0.85).
In study 331-10-231 the sample size of the brexpiprazole 0.25 mg/day group was set at 90 subjects, resulting in a power less than 70%, the Applicant was not expecting a clinically meaningful effect at the dose of 0.25 mg and the imalanced randomization was motivated by safety/ethical reasons.
The second phase 3 short term pivotal study (331-10-**230**) supports an effect of brexpiprazole in reducing schizophrenia symptoms as measured by the PANSS but only at the dose of 4 mg.
During the trial, patients on brexpiprazole 4mg improved significantly after 6 weeks as compared to placebo patients (LS mean -20 points; -13.53, respectively). The groups treated with the dose of 1mg and 2 mg showed similar numeric improvement (-16.9, -16.6 respectively) despite this being not statistically significant. Of note, in this trial, the randomization was unbalanced and the 1 mg arm counted only 117 patients, this number however allowed a fully powered statistical analysis.
The onset of efficacy, when measured at the PANSS, was already significant at week 1, but only in the 4 mg arm.
The difference in CGI-S scores between treatment and placebo showed a similar pattern where only patients in the 4mg arm separated significantly from placebo (-1.19 LS mean vs -0.81 treatment and placebo respectively). Numeric improvement in the 2mg and 1mg arms was similar.
In the regional phase 3 study (331-10-**002**) results support the efficacy of brexpiprazole in reducing schizophrenia symptoms as measured by the PANSS but only at the dose of 2 mg.
Several Amendments were implemented after trial initiation date (07 Dec 2011) and before trial Completion (07 Jul 2015). Amendments of 09 Oct 2012 and 24 Dec 2014 lead to several modifications in the analysis method.
The Applicant provided the rationale and the content of all the amendments of the study 331-10-002, reassuring that all the changes in statistical analysis plan were done to match the revised protocol of the global trial (the bridging target trial). Moreover, the Applicant also provided the comparison of the

results of the primary analysis conducted according to the final protocol, i.e. by MMRM and using multiple comparison procedure, with those of primary analysis as originally planned, i.e. ANCOVA model with LOCF imputation and the Hochberg procedure for the multiplicity control method (already available in the submitted documentation), in order to prove that the change did not impact on the conclusion of the study. The additional information is reassuring on the conduct of the analysis and on the conclusion of the study that remains unchanged.
Of note, during this trial, the placebo group improved less than in the global studies (230&231) with a LS mean change at week 6 of -7.63 at the PANSS. The group treated with 2 mg improved substantially (LS mean change -14.95, p = 0.0124) and kept the statistical significance also with the Hochberg procedure. This difference appeared at week 3 of treatment and remained through the study period. The group treated with 4 mg improved less (-3.86 difference from placebo, not statistically significant). The lowest numerical improvement was observed in the group treated with 1mg.
Analyses of the CGI-S showed no significant difference from placebo and this is a key element to judge efficacy. Of note, it is reminded that since in the primary analysis, only the 2 mg dose arm showed statistically significant separation from placebo, secondary analyses can be considered only supportive from a statistical point of view.
In a clinical perspective, it is noted that the analyses of secondary outcomes shows an effect on the negative symptoms domain, both at the PANSS negative subscale (LS mean was −3.48 in the 2 mg group and −3.24 in the 4 mg group, vs −1.20 in the placebo group) and at the Marder factor score negative symptoms where the 2 and 4 mg groups separated from placebo; the 2 mg group separated from placebo also in the disorganized though factor. In the positive symptom factor there was no separation from placebo.
To assess the comparability of the results between the regional and the global trials, the frequencies of UR, EM, IM and PM (for the CYP2D6 genotype) were calculated and resulted highly comparable, therefore it is unlikely that the inconsistency of the pivotal efficacy results with respect to brexpiprazole doses may depend on pharmacogenomic issues.
Additional analyses of the regional Japanese trial revealed that gender distribution and mean age differed as compared to the global trials. As such, a posthoc analysis was conducted to further explore these differences. The results of this analysis show that when age and gender are added as fixed effects to the MMRM model, brexpiprazole 4 mg/day separates from placebo ($p < 0.05$) at Week 3 (−5.05, p = 0.0337), Week 4 (−7.18, p = 0.0082), and Week 5 (−6.07, p = 0.0420). At Week 6, a trend towards statistical separation is observed (−5.59, p = 0.0710).
In the flexible dose, active and placebo controlled study **14644A,** the group treated with the dose range of 2-4 mg brexpiprazole failed to separate from placebo at the primary endpoint. Placebo patients showed a reduction in PANSS total scores at week 6 of -15.9 (higher than what seen in the fixed dose phase 3 trials), therefore the improvement with brexpiprazole (LS mean change -20) was not sufficient to achieve statistical difference, whilst patients treated with flexible doses of quetiapine XR improved on average by -24 points therefore this different was statistically significant in comparison to placebo.
The failure of the brexpiprazole group to separate from placebo was confirmed in several sensitivity analyses, however when using OC ANCOVA or LOCF ANCOVA the results were statistically significant. It is to be noted that the ANCOVA is not considered a conservative approach in this context.

When measuring the differences in reduction of PANSS total scores between the brexpiprazole group and the placebo group at weeks 2, 3 and 4, the difference was statistically significant, confirming an onset of therapeutic effect at week two, like most antipsychotics.
The difference in CGI-S scores between the brexpiprazole group and placebo was statistically significant (LS mean -1.2 vs -0.9 for placebo, p = 0.0142), although the numeric improvement was slightly inferior to that of the quetiapine group (LS mean -1.4, p = 0.0002). However, the primary and the key

secondary endpoints had to be tested hierarchically. Therefore, since the primary endpoint was not statistically significant (p = 0.056), the analysis of the key secondary endpoint should not to be formally considered.
A limitation in the assessment of efficacy comes from the fact that both active comparator studies 203 (dose response) and 14644A were negative for brexpiprazole. While in study 203 a comparison between brexpiprazole and ariprazole was not possible, in study 14644A assay sensitivity was demonstrated and in all comparisons, including the sensitivity analyses, the magnitude of PANSS scores reduction was greater for the quetiapine group than for the brexpiprazole group.
The applicant carried out additional analyses of responders and looked into significance of CGI-I and Personal and Social Performance scale scores. The responder analysis uses relative risk to demonstrate that both quetiapine and brexpiprazole differentiate from placebo, which is shown for reduction in PANSS scores ≥30% and ≥40% but not for ≥50% which failed for both active treatments. The change in Personal and Social Performance scale and CGI-I are statistically significant.

Table 12 Trial 14644A ITT Responder Analysis: PANSS Total Score Reduction at Week 6 (Efficacy Sample)

Table 5.1.3.1.2-2 Trial 14644A ITT Responder Analysis: PANSS Total Score Reduction at Week 6 (Efficacy Sample)						
Reduction	**Treatment**	**n**	**n (%)**	**Relative[a] Risk**	**95% CI[a]**	**p-value[a]**
≥ 30%	BREX 2-4 mg	150	74 (49.33)	1.45	(1.11, 1.88)	0.0044
	QUET	150	85 (56.67)	1.59	(1.25, 2.03)	0.0001
	Placebo	159	55 (34.59)	--	--	--
≥ 40%	BREX 2-4 mg	150	51 (34.00)	1.63	(1.14, 2.33)	0.0061
	QUET	150	55 (36.67)	1.68	(1.18, 2.40)	0.0028
	Placebo	159	33 (20.75)	--	--	--
≥ 50%	BREX 2-4 mg	150	27 (18.00)	1.45	(0.87, 2.41)	0.1429
	QUET	150	32 (21.33)	1.61	(0.98, 2.64)	0.0525
	Placebo	159	20 (12.58)	--	--	--

In addition to the pre-specified analyses assuming missing data to be MNAR, to further investigate the potential impact of missing data being MNAR in the conclusions of these trials, an estimand of treatment-policy with a hypothetical strategy as if other medications had not been available for use was considered. In this estimand, all subjects who discontinued brexpiprazole are considered as falling 'back to placebo' from the time of discontinuation onwards because of the intended symptomatic improvement of the trial medication. Thus, missing data were imputed using placebo based multiple imputation (PMI) to construct back to placebo analysis for all subjects who discontinued, ie, in addition to missing data in placebo group, missing observations in the brexpiprazole groups were imputed

following a model not from the observed data in brexpiprazole groups but rather from the observed data in the placebo group.
As shown in Table , the PMI 'back to placebo' analysis of the primary endpoint of change from baseline in PANSS Total Score to Week 6 showed consistent results and a similar magnitude of treatment effect (point estimate) as that observed in the pre-specified MMRM primary analysis. So do the CGI and most secondary endpoints.

Table 13 MNAR Using Placebo Multiple Imputation in PaNSS Total Score at Week 6, Efficacy sample

Table 5.2.3.1-1 MNAR Using Placebo Multiple Imputation in PANSS Total Score at Week 6, Efficacy Sample				
Trial Treatment Group	Treatment Comparison versus Placebo[a]			
	Treatment Difference	95% CI Lower Limit	95% CI Upper Limit	P-value
331-10-231				
Brex 0.25 mg	-1.752	-7.272	3.769	0.5339
Brex 2 mg	-7.550	-12.087	-3.012	0.0011
Brex 4 mg	-7.365	-11.869	-2.860	0.0014
331-10-230				
Brex 1 mg	-2.825	-7.787	2.136	0.2643
Brex 2 mg	-2.760	-7.121	1.602	0.2148
Brex 4 mg	-5.550	-9.996	-1.103	0.0145
331-10-002				
Brex 1 mg	-1.495	-8.404	5.415	0.6715
Brex 2 mg	-8.802	-15.421	-2.184	0.0092
Brex 4 mg	-4.871	-11.589	1.846	0.1552
14644A				
Brex 2-4 mg	-3.703	-7.555	0.149	0.0595
Quet	-6.436	-10.320	-2.553	0.0012

Brex = brexpiprazole; CI = confidence interval; Quet = quetapine XR.
Note: Placebo multiple imputation was based on monotone missing data structure of the observations using control-based pattern imputation in PROC MI. Monotone missing data structure was achieved using MCMC option of PROC MI.
For each imputed data, ANCOVA with treatment and (pooled) center as effects and baseline value as a covariate was used.
[a]Derived based on 100 imputations.
Source: Appendix 2, Day 180 Q19-1.

Maintenance of effect was investigated in the relapse prevention trial (331-10-**232**).
The study was stopped at the first interim analysis for demonstration of efficacy, indeed, relapses were significantly delayed in the brexpiprazole group as compared to placebo (p = 0.0008) and subjects treated with brexpiprazole had 66% lower risk of experiencing impending relapse compared to placebo. The criteria pre-specified needed for making an efficacy claim at the first interim analysis in study 232 were met. The interim analysis was conducted when 45 events occurred (13 Oct 2014) and a final analysis was also performed based on 53 events as additional 8 impending relapse events occurred during the time period from 13 Oct 2014 to 14 Jan 2015 (last visit in the Double-blind Maintenance phase).

In addition, it was initially unclear if subjects randomized to placebo had been discontinued from brexpiprazole abruptly or gradually. The Applicant clarified that acute events or any reaction that could be attributable to a rebound effect were unlikely to have contributed to the results of study 232, even though treatment discontinuation was abrupt. First of all brexpiprazole has a long half-life; second, the Kaplan Meier curves started separating after 28 days and; third, events that occurred in the first 4 weeks of the double blind phase were censored in a sensitivity analysis which is presented.
The sensitivity analysis demonstrated efficacy in maintenance of treatment effect similarly to the primary analysis, with time to impending relapse significantly delayed with brexpiprazole as compared to placebo (p = 0.0003).
The overall discontinuation rate from the Stabilization Phase was 56.5% (262 of 464 subjects). Of all subjects who discontinued from the trial, approximately 38% (176 of 464) discontinued due to a specific cause while the remaining 18.5% (86 of 464) discontinued due to sponsor termination of the trial. The most frequently reported reasons for discontinuation due to a specific cause from the Stabilization Phase were: subject withdrew consent to participate (n = 60; 12.9%), AE without impending relapse (n = 43; 9.3%), subject met (protocol-specified) withdrawal criteria (n = 22; 4.7%) and lack of efficacy (n = 21; 4.5%).
Results of other secondary endpoints (evaluated for final analyses only) supported the efficacy of brexpiprazole 1 to 4 mg/day in the maintenance treatment of schizophrenia. These included a larger proportion of subjects meeting stability criteria, improvement in clinical symptomology (as assessed by PANSS, CGI-S, and CGI-I [ANOVA, LOCF]), improved functioning (as assessed by PSP and GAF scales [ANOVA, LOCF]), and prolonged time to trial discontinuation, as compared with placebo.
The proportion of subjects who continued to meet criteria for stability at the last visit in the Double-blind Maintenance phase was 79.17% in the brexpiprazole group compared with 56.73% in the placebo group (p = 0.0007). The mean PANSS Total Score was maintained during the Double-blind Maintenance phase in subjects randomised to brexpiprazole; whereas, mean scores worsened for subjects randomized to placebo. Comparable results were observed in mean change from baseline on the PANSS Positive and Negative Subscale scores and Marder Factor scores, PEC, CGI-S, and CGI-I scores at endpoint. The PSP and GAF scales, which assess functioning, were supportive of the efficacy of brexpiprazole treatment, as was the time to trial discontinuation (for reasons other than termination of the trial for positive interim analysis).

2.5.4. Conclusions on the clinical efficacy

Evidence of efficacy for brexpiprazole comes from the three short-term, placebo-controlled pivotal studies 331-10-231, 331-10-230, 331-10-002. The first pivotal phase 3 study (231) supports efficacy of brexpiprazole at the doses of 2 and 4 mg/day in terms of reduction of symptoms as measured by the PANSS and confirmed by the CGI, key secondary endpoint. The second phase 3 short term pivotal study (230) supports an effect of brexpiprazole in reducing schizophrenia symptoms as measured by the PANSS but only at the dose of 4 mg. In the regional phase 3 study (002) results support the efficacy of brexpiprazole in reducing schizophrenia symptoms as measured by the PANSS but only at the dose of 2 mg. In the flexible dose, active and placebo controlled study 14644A, the group treated with the dose range of 2-4 mg brexpiprazole failed to separate from placebo at the primary endpoint, whilst patients treated with flexible doses of quetiapine XR improved in a statistically significant fashion. The numerical improvement as measured by mean reduction of PANSS scores is similar in all global trials and considered clinically relevant.
The assumptions on the missing data handling, should provide a realistic description of the treatment effect to enable patients and prescribers to make informed choices at point of prescription. For this reason the Applicant presented a secondary analysis using an MMRM approach with PMI imputation.

Results from the primary and secondary analysis were consistent and results showed a similar magnitude of treatment effect (point estimates) for primary and secondary endpoints.
The relapse prevention trial (232), was stopped at the first interim analysis for demonstration of efficacy. A clear dose-response was not observed in the short term studies, which is compatible with results from similar development programs of antipsychotics, a dose response curve is evident when pooling the two global trials A concern in the assessment of efficacy arises also from the fact that both active comparator studies 203 (dose response) and 14644A were negative for brexpiprazole. While in study 203 a comparison between brexpiprazole and aripiprazole was not possible, in study 14644A assay sensitivity was demonstrated and in all comparisons, including the sensitivity analyses, the magnitude of PANSS scores reduction was greater for the quetiapine group than for the brexpiprazole group. No further direct comparisons with other second-generation antipsychotics are available.

2.1. Clinical safety

Table 14 Brexpiprazole Safety Analysis Groups through 31 Aug 2016

All Schizophrenia Trials	
Short-term, Controlled Trials	Pooled data under 3 integrated dose groups (< 2 mg/day, 2 to 4 mg/day, and > 4 mg/day) and placebo, plus an all brexpiprazole treatment group[a] combining data from 4 phase 3 trials (331-10-231, 331-10-230, 331-10-002, 14644A) and 1 phase 2 trial (331-07-203)
	Pooled data by fixed dose (1 mg/day, 2 mg/day, and 4 mg/day) and placebo from 3 phase 3 fixed-dose trials (331-10-230, 331-10-231, 331-10-002)
Long-term, Controlled Trial	Data presented separately for 1 - 4 mg/day and placebo groups in the randomized, Double-blind Maintenance phase of Trial 331-10-232, which included only those subjects enrolled in the Single-blind Stabilization phase who met stability criteria for randomization
Long-term, Open-label Trials	Pooled data from 4 completed trials (331-08-210[b], 331-10-237, 14644B, and 331-10-003) including subjects with no prior exposure to brexpiprazole (de novo) and rollover subjects from one of the parent trials (331-10-237[c] from 331-10-230, 331-10-231, 331-10-232; 331-10-003 from 331-10-002; and 14644B from 14644A) who received double-blind treatment (brexpiprazole, placebo, or active reference) for 6 weeks
All Trials	
All Brexpiprazole Trials	Pooled data[d] in 32 phase 2/3 completed and ongoing trials in schizophrenia (13 trials), MDD (17 trials), ADHD (1 trial), and PTSD (1 trial) exposed to at least 1 dose of brexpiprazole
All Clinical Pharmacology Trials	Pooled data from diverse populations (male and female subjects, healthy subjects, subjects with psychiatric diseases (schizophrenia, MDD, and ADHD), subjects with hepatic or renal impairment, and elderly subjects (with and without MDD); includes 15 trials conducted in healthy subjects, 4 schizophrenia trials, 2 MDD trials, 1 ADHD trial, and 2 trials conducted in special populations hepatic or renal impairment
Ongoing Trials	Individual trial data (exposure, deaths, serious TEAEs, AEs leading to discontinuation, and pregnancies) from 5 trials presented separately, by trial, in MDD (2 trials) and agitation associated with dementia of the Alzheimer's type (3 trials)
Ongoing Trials	Individual trial data (exposure, deaths, serious TEAEs, AEs leading to discontinuation, and pregnancies) from 5 trials presented separately, by trial, in MDD (2 trials) and agitation associated with dementia of the Alzheimer's type (3 trials)

ADHD = attention deficit hyperactivity disorder; PTSD = post-traumatic stress disorder
[a]The all brexpiprazole treatment group includes all subjects receiving brexpiprazole in the short-term, controlled trials regardless of dose.
[b]Trial 331-08-210 was originally 6 weeks in duration and later amended to 52 weeks. Subjects who completed Trial 331-08-210 prior to the protocol amendment were not included in the long-term, open-label group.

[c]Subjects pooled from Trial 331-10-237 include only those with 52-weeks of trial duration (before the 26-week protocol amendment).
[d]Includes subjects completing 6 weeks in long-term, open-label Trial 331-08-210 prior to the protocol amendment that changed the duration of the trial from 6 to 52 weeks and were not included in the long-term Safety Sample.

Patient exposure

The data cutoff date for trials included in the safety analyses was 31 Aug 2016.

Short term controlled trials:

Table 15 Treatment Duration and Overall Exposure (Safety Sample: Short term, Controlled Trials–Schizophrenia)

Table 2.7.4.1.2.1-1 Treatment Duration and Overall Exposure (Safety Sample: Short-term, Controlled Trials - Schizophrenia)

Exposure Parameter	Brexpiprazole				
	< 2 mg (N = 456)	2 - 4 mg (N = 1199)	> 4 mg (N = 93)	All (N = 1748)	Placebo (N = 740)
Treatment duration (days)					
n	456	1199	93	1748	740
Mean (SD)	33.3 (13.0)	34.5 (12.4)	33.5 (12.5)	34.1 (12.6)	32.9 (13.2)
Min, Max	1, 47	1, 45	1, 44	1, 47	1, 46
Treatment duration, n (%)					
≥ 1 day	456 (100.0)	1199 (100.0)	93 (100.0)	1748 (100.0)	740 (100.0)
≥ 7 days	436 (95.6)	1152 (96.1)	89 (95.7)	1677 (95.9)	704 (95.1)
≥ 21 days	363 (79.6)	979 (81.7)	77 (82.8)	1419 (81.2)	573 (77.4)
≥ 42 days	247 (54.2)	686 (57.2)	53 (57.0)	986 (56.4)	375 (50.7)

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-5.1.6 and CT-ST-SZ-5.2.1.

Table 16 Summary of Subject Disposition (Randomized Sample: Short-term, Controlled Trials –Schizophrenia)

Table 2.7.4.1.2.8.1-1 Summary of Subject Disposition (Randomized Sample: Short-term, Controlled Trials - Schizophrenia)

Completion Status	Number (%) of Subjects						
Disposition Event	Brexpiprazole				Placebo	ARI	QUET
	< 2 mg (N = 456)	2 - 4 mg (N = 1201)	> 4 mg (N = 93)	All (N = 1750)	(N = 742)	(N = 50)	(N = 154)
Completed	281 (61.6)	819 (68.2)	56 (60.2)	1156 (66.1)	458 (61.7)	34 (68.0)	122 (79.2)
Switched to Open Label	24 (5.3)	11 (0.9)	11 (11.8)	46 (2.6)	15 (2.0)	4 (8.0)	0 (0.0)
Discontinued	151 (33.1)	371 (30.9)	26 (28.0)	548 (31.3)	269 (36.3)	12 (24.0)	32 (20.8)
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	1 (2.0)	0 (0.0)
Adverse Events	49 (10.7)	105 (8.7)	11 (11.8)	165 (9.4)	91 (12.3)	3 (6.0)	4 (2.6)
Met Protocol-specified Withdrawal Criteria	2 (0.4)	5 (0.4)	0 (0.0)	7 (0.4)	2 (0.3)	0 (0.0)	0 (0.0)
Withdrawn by Investigator	4 (0.9)	3 (0.2)	0 (0.0)	7 (0.4)	4 (0.5)	0 (0.0)	0 (0.0)
Withdrew Consent	60 (13.2)	145 (12.1)	11 (11.8)	216 (12.3)	80 (10.8)	4 (8.0)	6 (3.9)
Protocol Deviation	4 (0.9)	6 (0.5)	0 (0.0)	10 (0.6)	1 (0.1)	0 (0.0)	1 (0.6)
Lack of Efficacy	32 (7.0)	93 (7.7)	4 (4.3)	129 (7.4)	78 (10.5)	4 (8.0)	11 (7.1)
Other	0 (0.0)	14 (1.2)	0 (0.0)	14 (0.8)	11 (1.5)	0 (0.0)	10 (6.5)

ARI = aripiprazole; QUET = quetiapine.
Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-2.1.

The three fixed-dose short term schizophrenia trials included 1284 patients treated with brexpiprazole (0.25 mg: n=90; 1 mg: n=235; 2 mg: n= 482; 4 mg: n= 477) and 484 patients treated with PBO.

In the five short-term, controlled trials, the mean (SD) brexpiprazole dose for those 1199 subjects randomized to receive a dose in the range of 2 to 4 mg/day was 2.7 mg/day (0.8). For the all brexpiprazole treatment group, the most frequent modal and final dose was brexpiprazole 4 mg/day.

In the flexible dose 6 weeks controlled study 14644A (active reference quetiapine XR), the average modal and mean doses of brexpiprazole were 3.8 mg/day and 3.5 mg/day, respectively, and the average modal and mean doses of quetiapine were 697 mg/day and 674 mg/day, respectively. 83% of the patients in the brexpiprazole group and 65% of the patients in the quetiapine group reached the high dose of IMP.

In the fixed dose Phase 2 Study 331-07-203 (active reference aripiprazole XR), the average daily dose at the end of double-blind treatment was as follows: 0.25 mg in the 0.25 mg/day in the brexpiprazole fixed-dose group; 1.30 mg in the 1.0 ± 0.5 mg/day brexpiprazole group; 2.74 mg in the 2.5 ± 0.5 mg/day brexpiprazole group; 5.45 mg in the 5.0 ± 1.0 mg/day brexpiprazole group; 16.58 mg in the aripiprazole 15 ± 5 mg/day group. In addition to double-blind treatment, 65 subjects received open-label brexpiprazole for ≤ 21 days in the non-responder open-label arm. More than half of the subjects who entered the open-label arm (40/65 subjects, 61.5%) received brexpiprazole for a duration of 15 to 21 days. The average daily dose of brexpiprazole during open-label treatment was 2.79 mg.

Table 17 Summary Brexpriprazole Treatment Duration and Dosing (Safety Sample: Short-term, Controlled Long-term Controlled and Log-term, Open-label Trials – Schizophrenia)

Table 2.7.4.1.2-1	Summary of Brexpiprazole Treatment Duration and Dosing (Safety Sample: Short-term, Controlled, Long-term Controlled and Long-term, Open-label Trials - Schizophrenia)		
	Short-term, Controlled	Long-term, Controlled	Long-term[a], Open-label
	Brexpiprazole All (N = 1748)	Brexpiprazole All (N = 97)	Brexpiprazole All (N = 1426)
Treatment Duration (days)			
Mean (SD)	34.1 (12.6)	172.2 (122.8)	229.2 (146.1)
Min, Max	1, 47	2, 369	1, 396
≥ 26 weeks	--	77 (79.3)	846 (59.3)
≥ 52 weeks	--	41 (42.2)	654 (45.8)
Mean Dose (mg/day)			
Mean (SD)	2.3 (1.3)	3.6 (0.7)	3.1 (0.8)
Min, Max	0.1, 5.7	1, 4	0, 5.9
Modal Daily Dose (%)			
< 1 mg/day	133 (7.6)	2 (2.1)	--
1 mg/day	319 (18.2)	1 (1.0)	33 (2.3)
2 mg/day	541 (30.9)	7 (7.2)	442 (31.0)
3 mg/day	122 (7.0)	25 (25.8)	279 (19.6)
4 mg/day	544 (31.1)	62 (63.9)	663 (46.5)
> 4 mg/day	89 (5.1)	--	8 (0.6)

Max = maximum; Min = minimum; SD = standard deviation.

[a]Long-term data include treatment from first dose in the long-term, open-label trials; previous treatment in a parent trial is not included.

Note: ≥ 52 weeks was defined as ≥ 360 days.

Note: Doses during up-titration were incorporated into the calculations of minimum and maximum doses.

Note: Modal dose was the dose most frequently taken by the subject.

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-5.1.6, CT-ST-SZ-5.2.1, CT-ST-SZ-5.2.2, CT-ST-SZ-5.2.3; Appendix 5, CT-LC-SZ-5.1.1, CT-LC-SZ-5.1.6, CT-LC-SZ-5.2.2, CT-LC-SZ-5.2.3; Appendix 6, CT-LT-SZ-5.1.1, CT-LT-SZ-5.1.6, CT-LT-SZ-5.2 and CT-LT-SZ-5.3.

Exposure in Long-term, Controlled Trial 331-10-232

Of the 464 subjects who received brexpiprazole monotherapy during the Single-blind Stabilization phase of Trial 331-10-232 (Phase B), 202 subjects were randomized into the Double-blind Maintenance phase (Phase C).

Table 18 Extent of Exposure(Cumulative) in Double-blind, Maintenance Phase C of Trial 331-10-232 (Randomised Sample)

Table 2.7.4.1.2.2-2 Extent of Exposure (Cumulative) in Double-blind, Maintenance Phase C of Trial 331-10-232 (Randomized Sample)			
Duration of Exposure [a]	**Brexpiprazole (1 - 4 mg) (N = 97)**	**Placebo (N = 105)**	**Total (N = 202)**
2 Weeks (1 - 14 days)	97 (100.0)	104 (99.0)	201 (99.5)
4 Weeks (15 - 28 days)	91 (93.8)	98 (93.3)	189 (93.6)
6 Weeks (29 - 42 days)	84 (86.6)	88 (83.8)	172 (85.1)
8 Weeks (43 - 56 days)	76 (78.4)	77 (73.3)	153 (75.7)
12 Weeks (57 - 84 days)	72 (74.2)	69 (65.7)	141 (69.8)
16 Weeks (85 - 112 days)	62 (63.9)	56 (53.3)	118 (58.4)
20 Weeks (113 - 140 days)	55 (56.7)	48 (45.7)	103 (51.0)
24 Weeks (141 - 168 days)	50 (51.5)	40 (38.1)	90 (44.6)
28 Weeks (169 - 196 days)	45 (46.4)	31 (29.5)	76 (37.6)
32 Weeks (197 - 224 days)	37 (38.1)	26 (24.8)	63 (31.2)
36 Weeks (225 - 252 days)	34 (35.1)	24 (22.9)	58 (28.7)
40 Weeks (253 - 280 days)	24 (24.7)	20 (19.0)	44 (21.8)
44 Weeks (281 - 308 days)	22 (22.7)	15 (14.3)	37 (18.3)
48 Weeks (309 - 336 days)	19 (19.6)	11 (10.5)	30 (14.9)
52 Weeks (337 - 364 days)	16 (16.5)	9 (8.6)	25 (12.4)
> 52 Weeks (≥ 365 days)	6 (6.2)	1 (1.0)	7 (3.5)
Any Exposure	97 (100.0)	104 (99.0)	201 (99.5)

[a]Exposure was calculated as: IMP end date (Phase C) - IMP start date (Phase C) + 1.
Source: CSR 331-10-232, Section 14.1.1, CT-7.1.

The majority of subjects were exposed to brexpiprazole for a duration of 12 to 18 weeks during the Stabilization phase. During the Double-blind Maintenance phase, the majority of subjects had a cumulative exposure to IMP in the range of 2 weeks up to 28 weeks due to the early termination of the trial by the sponsor following the positive results of the interim analysis; no more than approximately 30% of subjects had a cumulative exposure ≥ 32 weeks. The last visit mean average daily dose of brexpiprazole was 3.427 mg for all subjects in the Stabilization phase and 3.557 mg for all subjects randomized to brexpiprazole in the Double-blind Maintenance phase. The mean modal dose was 3.567 mg/day, and the most common modal dose for subjects randomized to brexpiprazole was 4 mg/day (64 subjects, 66%), followed by 3 mg/day (25 subjects, 25.8%).

Exposure in Long-term, Open-label Trials Group – Schizophrenia

Table 19 Treatment Duration and Overall Exposure (Safety Sample: Long-term, Open-label Trials –Schizophrenia)

Table 2.7.4.1.2.3-1 Treatment Duration and Overall Exposure (Safety Sample: Long-term, Open-label Trials - Schizophrenia)	
Exposure Parameter	**Brexpiprazole (N = 1426)**
Treatment duration (days)	
n	1426
Mean (SD)	229.2 (146.1)
Min, Max	1, 396
Treatment duration, n (%)	
≥ 1 day	1425 (99.9)
≥ 1 week	1380 (96.7)
≥ 4 weeks	1260 (88.3)
≥ 8 weeks	1115 (78.1)
≥ 14 weeks	996 (69.8)
≥ 26 weeks	846 (59.3)
≥ 38 weeks	757 (53.0)
≥ 52 weeks	654 (45.8)

Source: Module 5.3.5.3, SCS, Appendix 6, CT-LT-SZ-5.1.1 and CT-LT-SZ-5.1.6.

In the long term, open label trials, the mean (SD) brexpiprazole dose was 3.1 mg/day (0.8). The mean (SD) dose in the completer population was 3.2 mg/day (0.8). The most frequent modal dose overall was 4 mg/day
(n = 663, 46.5% of subjects), followed by 2 mg/day (n = 442, 31.0% of subjects). At their final dose, the largest proportions of subjects had brexpiprazole 4 mg/day (n =702, 49.3%) or 2 mg/day (n = 368, 25.8%). For the completer population, the most frequent modal doses were also 4 mg/day (52.9%), and 2 mg/day and 3 mg/day (both 22.2%); the 2 most frequent final doses were 4 mg/day (52.7%) and 3 mg/day (22.2%).
The mean brexpiprazole dose by treatment duration reached 3.22 mg/day among subjects with ≥ 4 weeks of exposure, and 3.28 mg/day among subjects with ≥ 52 weeks of exposure. The overall mean dose was 2.99 mg/day, and the mean endpoint dose (last nonmissing dose taken during the trial) was 3.29 mg/day.

Table 20 Composition of Long-term, Open-label Trials Group

Table 2.7.4.1.2.8.3-1 Composition of Long-term, Open-label Trials Group					
Treatment Group:	Parent Trials				Total OL Brexpiprazole[a] (N = 1426)
	Trial 14644B (N = 206)	Trial 331-08-210 (N = 28)	Trial 331-10-003 (N = 281)	Trial 331-10-237 (N = 911)	
Rollover subjects	206	28	98	687	1019
Prior placebo	63	6	28	181	278
Prior aripiprazole	0	2	0	0	2
Prior quet	79	0	0	0	79
Prior brexpiprazole	64	20	70	506	660
De novo subjects	0	0	183	224	407

OL = open-label.

[a]Subjects pooled from Trial 331-10-237 include only those with 52-weeks of trial duration (before the 26-week protocol amendment).

De novo subjects were subjects with no prior exposure to brexpiprazole.

Source: Module 5.3.5.3, SCS, Appendix 6, CT-LT-SZ-1.1.1 and CT-LT-SZ-1.1.2.

Of the 1426 subjects who received brexpiprazole in the long term, open label trials, 428 were enrolled in North America, 574 in Europe, 334 in Asia, and 90 in Latin America. The percentage of subjects who discontinued from the trials was higher for subjects enrolled at sites in North America (68.5%) than subjects at sites in Europe (43.2%), Latin America (52.2%), and Asia (47.0%). Frequently cited reasons for discontinuation in all regions were "AEs" and "withdrawal of consent." Subjects withdrawing because they "met protocol specified withdrawal criteria" was the primary difference in discontinuation rates between sites in North America and other regions, with a higher percentage of subjects at North American sites withdrawing for this reason (14.0%) than at sites in Europe (1.4%), Latin America (4.4%), and Asia (3.0%). A higher percentage of US subjects met the withdrawal criteria for illicit substance abuse (7.0%) and/or noncompliance with visit windows (5.6%), resulting in a larger proportion of US subjects being withdrawn from the trials, compared with subjects from the rest of the World.

Table 21 Number and Percentage of Subjects Who Received Brexpiprazole by Overall Mean Dose Category and Duration of Exposure (Safety Sample:Schizophrenia Phase 2/3 Brexpiprazole Trials)

	1 MG		2 MG		3 MG		4 MG		>4 MG		TOTAL	
EXPOSURE	(N=402)		(N=759)		(N=810)		(N=903)		(N=296)		(N=3170)	
PARAMETER	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
<4 WEEKS	199	(49.5)	182	(24.0)	125	(15.4)	23	(2.5)	98	(33.1)	627	(19.8)
4-8 WEEKS	164	(40.8)	234	(30.8)	197	(24.3)	212	(23.5)	76	(25.7)	883	(27.9)
8-14 WEEKS	22	(5.5)	88	(11.6)	128	(15.8)	72	(8.0)	56	(18.9)	366	(11.5)
14-26 WEEKS	3	(0.7)	55	(7.2)	104	(12.8)	85	(9.4)	13	(4.4)	260	(8.2)
26-38 WEEKS	3	(0.7)	32	(4.2)	49	(6.0)	89	(9.9)	4	(1.4)	177	(5.6)
38-52 WEEKS	1	(0.2)	21	(2.8)	38	(4.7)	72	(8.0)	4	(1.4)	136	(4.3)
52-78 WEEKS	10	(2.5)	143	(18.8)	159	(19.6)	316	(35.0)	45	(15.2)	673	(21.2)
78-104 WEEKS	0	(0.0)	2	(0.3)	7	(0.9)	22	(2.4)	0	(0.0)	31	(1.0)
>= 104 WEEKS	0	(0.0)	2	(0.3)	3	(0.4)	12	(1.3)	0	(0.0)	17	(0.5)
ANY EXPOSURE	402	(100.0)	759	(100.0)	810	(100.0)	903	(100.0)	296	(100.0)	3170	(100.0)

Exposure in the All Brexpiprazole Trials Group

Table 22 Treatment Duration and Overall Exposure (Saftey Sample: All Brexpiprazole Trials Group)

Table 2.7.4.1.2.4-1 Treatment Duration and Overall Exposure (Safety Sample: All Brexpiprazole Trials Group)					
Exposure Parameter	Number (%) of Brexpiprazole Subjects				
	Schizophrenia (N = 3170)	Major Depressive Disorder (N = 3672)	ADHD (N = 155)	PTSD (N = 23)	All Brexpiprazole (N = 7020)
	SCH	MDD	ADHD	PTSD	BREX
≥ 1 DAY	3170 (100.0)	3672 (100.0)	155 (100.0)	23 (100.0)	7020 (100.0)
≥ 1 WEEK	3061 (96.6)	3634 (99.0)	155 (100.0)	22 (95.7)	6872 (97.9)
≥ 4 WEEKS	2543 (80.2)	3415 (93.0)	149 (96.1)	20 (87.0)	6127 (87.3)
≥ 8 WEEKS	1660 (52.4)	2630 (71.6)	0 (0.0)	19 (82.6)	4309 (61.4)
≥ 14 WEEKS	1294 (40.8)	2147 (58.5)	0 (0.0)	14 (60.9)	3455 (49.2)
≥ 26 WEEKS	1034 (32.6)	1376 (37.5)	0 (0.0)	0 (0.0)	2410 (34.3)
≥ 38 WEEKS	857 (27.0)	1142 (31.1)	0 (0.0)	0 (0.0)	1999 (28.5)
≥ 52 WEEKS	721 (22.7)	1012 (27.6)	0 (0.0)	0 (0.0)	1733 (24.7)
≥ 78 WEEKS	48 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	48 (0.7)
≥ 104 WEEKS	17 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	17 (0.2)

SCH = schizophrenia
Source: Module 5.3.5.3, SCS, Appendix 7, CT-ALL-1.1.1.

Overall, 2263 subjects were exposed to 1 mg (< 1.5 mg) brexpiprazole across indications (schizophrenia, MDD, ADHD, PTSD). The majority of subjects (n = 4459) were exposed to brexpiprazole within the proposed therapeutic dose range (2 to 4 mg/day); 1981 subjects were exposed to 2 mg (≥ 1.5 to < 2.5 mg) doses, 1574 subjects were exposed to 3 mg (≥ 2.5 to < 3.5 mg) doses, and 904 subjects were exposed to 4 mg (≥ 3.5 to ≤ 4.5 mg) doses of brexpiprazole. A total of 298 subjects received doses of brexpiprazole > 4 mg (> 4.5 mg).

Exposure in Clinical Pharmacology Trials

Across all the clinical pharmacology trials, 877 subjects received treatment with brexpiprazole either alone or concomitantly with another product (eg, antidepressant therapy or stimulant). Across the trials, the majority of the subjects were exposed to a dose of brexpiprazole 1 to 4 mg/day.

Overall, a majority (88.8%) of the subjects completed the trials. The most frequently reported reasons for discontinuation were "withdrawal of consent" (4.3%) and "AEs" (3.3%). Trial 331-08-206 was terminated by the sponsor before completion of the trial because the protocol-specified tolerability criteria were met for the 3 mg dose. Enrollment and dosing in Trial 331-08-208 Group 4 were terminated prior to completion of the trial by the sponsor; no safety concerns were identified.

Exposure in Ongoing Trials

Table 23 Number of Subjects Enrolled/Randomised by Trial for Ongoing Trials

Table 2.7.4.1.2.6-1 Number of Subjects Enrolled/Randomized by Trial for Ongoing Trials

Trial	Number enrolled/randomized	Open-label[a]	Double-blind
MDD			
331-12-282[b]	2177 enrolled/503 randomized		X
331-10-238[c]	2869 enrolled	X	
Agitation in AD			
331-12-283[d]	360 randomized		X
331-12-284[e]	188 randomized		X
331-13-211	261 enrolled	NA[f]	
Clinical Pharmacology			
331-10-233[g]	34 enrolled	X	

NA = not applicable

[a]All subjects enrolled in open-label trials are exposed to brexpiprazole, unless otherwise noted.

[b]Subjects in Trial 331-12-282 are randomized in a 2:2:1 ratio to receive continued adjunctive treatment with brexpiprazole, adjunctive treatment with Seroquel XR, or adjunctive with placebo treatment.

[c]Trial 331-10-238 includes rollover subjects from completed Trials 331-10-227 and 331-10-228 and ongoing Trial 331-12-282 (treatment assignments for Trial 331-12-282 were still blinded as of the data cutoff date). Unblinded data from these trials are included in the All Brex group.

[d]Subjects in Trial 331-12-283 are randomized 1:1:1 to brexpiprazole (1 or 2 mg brexpiprazole, or placebo).

[e]Subjects in Trial 331-12-284 are randomized to brexpiprazole or placebo (1:1).

[f]Trial 331-13-211 is an observational trial of subjects who previously received brexpiprazole or placebo in ongoing AD Trial 331-12-283 and Trial 331-12-284. No IMP is being administered during this trial.

[g]Trial 331-10-233 is an open-label dose-escalation trial being conducted in adolescent subjects.

Source: Tabular Listing of All Clinical Studies, Module 5.2.

Demographic and Baseline Characteristics of Study Population

In the short-term, controlled trials, both the demographic and baseline characteristics and psychiatric history parameters were similar across treatment groups. Demographic and baseline characteristics in the long-term, controlled and open-label trials were similar to those in the short-term, controlled trials, with the exception of mean weight, which was higher in the placebo group of the long-term controlled trial.

Table 24 Summary of Demographic and Baseline Characteristics and Psychiatric History (Randomised Sample: Short term, Controlled Trials and Long-term Controlled and Safety Sample: Long term, Open-label Trials – Schizophrenia)

Table 2.7.4.1.3-1 Summary of Demographic and Baseline Characteristics and Psychiatric History (Randomized Sample: Short-term, Controlled Trials and Long-term, Controlled and Safety Sample: Long-term, Open-label Trials - Schizophrenia)

	Short-term, Controlled				Long-term, Controlled		Long-term, Open-label
	BREX (N = 1750)	Placebo (N = 742)	ARI (N = 50)	QUET (N = 154)	BREX (N = 97)	Placebo (N = 104)	BREX (N = 1426)
Mean age (years)	40.1	40.5	40.8	41.1	38.8	41.6	41.2
Mean weight (kg)	74.8	74.9	72.9	81.8	79.3	84.9	77.2
Female n, %	709, 40.5	311, 41.9	16, 32.0	64, 41.6	39, 40.2	40, 38.5	627, 43.97
White n, %	906, 51.8	414, 55.8	34, 68.0	114, 74.0	62, 63.9	65, 62.5	754, 52.88
Mean age of first diagnosis (years)	26.7	26.6	26.8	27.3	--	--	--
Mean duration of current episode (weeks)	2.7	2.8	2.9	--	--	--	--

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-3.1.1, CT-ST-SZ-3.2; Appendix 5, CT-LC-SZ-3.1.1; and Appendix 6, CT-LT-SZ-3.1.1.

Medical History

In the short-term, controlled trials, medical history reported by ≥ 10% of subjects in the all brexpiprazole or placebo group, respectively, included insomnia (39.8% and 35.8%), agitation (30.0% and 30.5%), anxiety (17.5% and 15.4%), constipation (15.1% and 13.4%), headache (13.6% and 14.6%), and hypertension (10.8% and 11.6%).

In the long-term, controlled Trial 331-10-232, medical history of the randomized sample reported by ≥ 10% of subjects in the all brexpiprazole or placebo group, respectively, included agitation (12.4% and 9.6%), anxiety (12.4% and 14.4%), insomnia (26.8% and 29.8%), extrapyramidal disorder (10.3% and 2.9%) and hypertension (5.2% and 14.4%).

In the long-term, open-label trials, medical history (represented new medical history, ie, reported since the baseline of the parent trial, for all subjects except de novo subjects) reported by ≥ 2% of subjects included insomnia (13.0%), hypertension (6.7%), agitation (5.6%), anxiety (4.1%), headache (3.6%), obesity (3.4%), depressive symptom (2.7%), drug hypersensitivity (2.2%), akathisia (2.1%), back pain (2.1%), and extrapyramidal disorder (2.0%).

Adverse events

Short term controlled trials in schizophrenia

In the short-term, placebo-controlled trials in schizophrenia, a similar percentage of subjects reported ≥1 TEAE in the brexpiprazole 2 to 4 mg/day and placebo groups (60.7% and 62.2%, respectively). 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 headache (9.3%), akathisia (5.6%), weight increased (3.9%), nausea (3.6%), diarrhea (3.3%), tremor (2.7%), back pain (2.3%), dizziness (2.3%), blood creatine phosphokinase (CPK) increased (2.2%), and toothache (2.0%).

Among the most common TEAEs adverse events with brexpiprazole there were insomnia (9.2%) and agitation (5.3%), even though these events did not occur in higher percentage of patients on brexpiprazole compared to placebo

Table 25 Summary of Treatment-emergent Adverse Events (Safety Sample: Short-term, Controlled and Long -term, Open-label Trials - Schizophrenia)

TEAE Parameter	Number (%) of Subjects						
	Short-term, controlled				Long-term, controlled		Long-term, open-label
	BREX (N = 1748)	Placebo (N = 740)	ARI (N = 50)	QUET (N = 153)	BREX (N = 97)	Placebo (N = 104)	BREX (N = 1426)
Any TEAE	1083 (62.0)	460 (62.2)	35 (70.0)	101 (66.0)	42 (43.3)	58 (55.8)	951 (66.69)
Any severe TEAE	103 (5.9)	49 (6.6)	1 (2.0)	6 (3.9)	2 (2.1)	3 (2.9)	105 (7.36)
Any TEAE potentially related to IMP	608 (34.8)	244 (33.0)	21 (42.0)	82 (53.6)	14 (14.4)	25 (24.0)	529 (37.10)
Any death	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.35)
Any serious TEAE	59 (3.4)	31 (4.2)	2 (4.0)	2 (1.3)	3 (3.1)	11 (10.6)	193 (13.53)
Any TEAE leading to discontinuation of IMP	166 (9.5)	97 (13.1)	3 (6.0)	4 (2.6)	5 (5.2)	12 (11.5)	226 (15.85)

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-6.2.1, CT-ST-SZ-6.2.2.2, CT-ST-SZ-6.4, CT-ST-SZ-6.5.1, CT-ST-SZ-6.6.1, and CT-ST-SZ-6.7.1; Appendix 5, CT-LC-SZ-6.2.1, CT-LC-SZ-6.2.2.2, CT-LC-SZ-6.4; CT-LC-SZ-6.5.1, CT-LC-SZ-6.6.1, CT-LC-SZ-6.7.1; Appendix 6, CT-LT-SZ-6.2.1, CT-LT-SZ-6.2.4, CT-LT-SZ-6.4, CT-LT-SZ-6.5.1, CT-LT-SZ-6.6.1, and CT-LT-SZ-6.7.1.

Table 26 Incidence of TEAEs That Occurred in 2 - 4 mg Brex Group and ≥ 0.5% Greater Than That of Placebo Group by SOC and PT (Safety Sample: Short-term, Controlled Trials - Schizophrenia)

System Organ Class MedDRA Preferred Term	2 - 4 mg (N = 1199) n (%)	Placebo (N = 740) n (%)
Subjects With Any Treatment Emergent Adverse Events	728 (60.7)	460 (62.2)
Gastrointestinal Disorders		
Diarrhoea	39 (3.3)	13 (1.8)
Nausea	43 (3.6)	22 (3.0)
Abdominal Pain Upper	15 (1.3)	5 (0.7)
Dental Caries	7 (0.6)	1 (0.1)
Flatulence	9 (0.8)	1 (0.1)
General Disorders and Administration Site Conditions		
Pain	12 (1.0)	2 (0.3)
Investigations		
Weight Increased	47 (3.9)	15 (2.0)
Blood Creatine Phosphokinase Increased	26 (2.2)	8 (1.1)
Blood Pressure Increased	8 (0.7)	1 (0.1)
Blood Triglycerides Increased	6 (0.5)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	28 (2.3)	12 (1.6)
Pain In Extremity	20 (1.7)	9 (1.2)
Myalgia	11 (0.9)	3 (0.4)
Nervous System Disorders		
Akathisia	67 (5.6)	33 (4.5)
Tremor	32 (2.7)	9 (1.2)
Dizziness	28 (2.3)	10 (1.4)
Sedation	23 (1.9)	8 (1.1)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	7 (0.6)	0 (0.0)
Skin and Subcutaneous Tissue Disorders		
Rash	19 (1.6)	4 (0.5)

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-6.2.1 and CT-ST-SZ-6.3.11.

Table 27 TEAEs That Occurred in at Least 2% of Subjects in All Brexpiprazole Groups (1 to 4 mg/day) and Greater Than Placebo Group in Fixed-Dose Trials (Safety Sample: Schizophrenia)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects				
	Brexpiprazole				
	BREX 1mg (n = 235)	BREX 2mg (n = 482)	BREX 4mg (n = 477)	All (n = 1194)	Placebo (n = 484)
Subjects With Any Treatment Emergent Adverse Events	149 (63.4)	294 (61.0)	296 (62.1)	739 (61.9)	305 (63.0)
Gastrointestinal Disorders					
Diarrhoea	5 (2.1)	15 (3.1)	18 (3.8)	38 (3.2)	9 (1.9)
Dyspepsia	7 (3.0)	9 (1.9)	11 (2.3)	27 (2.3)	8 (1.7)
Infections and Infestations					
Nasopharyngitis	14 (6.0)	13 (2.7)	14 (2.9)	41 (3.4)	16 (3.3)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects				
	Brexpiprazole				
	BREX 1mg (n = 235)	BREX 2mg (n = 482)	BREX 4mg (n = 477)	All (n = 1194)	Placebo (n = 484)
Investigations					
Weight Increased	4 (1.7)	14 (2.9)	16 (3.4)	34 (2.8)	6 (1.2)
Blood Creatine Phosphokinase Increased	8 (3.4)	11 (2.3)	11 (2.3)	30 (2.5)	7 (1.4)
Musculoskeletal and Connective Tissue Disorders					
Back Pain	4 (1.7)	10 (2.1)	14 (2.9)	28 (2.3)	9 (1.9)
Nervous System Disorders					
Tremor	6 (2.6)	12 (2.5)	12 (2.5)	30 (2.5)	5 (1.0)

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-6.3.4.

Treatment-emergent Adverse Events in Long-term, Controlled Trial 331-10-232

In the Single-blind Stabilization phase of Trial 331-10-232 (Phase B) a total of 464 subjects were treated with brexpiprazole (1 - 4 mg/day). Of these subjects, 267 (57.5%) had TEAEs during the Stabilization 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. The incidence of TEAEs in the Psychiatric Disorders SOC was 9.3% in the brexpiprazole group compared with 24.0% in the placebo group.

Table 28 TEAEs with an Incidence of at Least 2% in the Brexpiprazole Group and Greater than Placebo in the Double-blind Maintenance Phase of Trial 331-10-232 (Safety Sample)

System Organ Class MedDRA Preferred Term	Brexpiprazole (1 - 4 mg) (N = 97) n (%)	Placebo (N = 104) n (%)
Gastrointestinal disorders		
Toothache	3 (3.1)	1 (1.0)
Metabolism and nutrition disorders		
Decreased appetite	2 (2.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Muscle spasms	2 (2.1)	0 (0.0)
Musculoskeletal pain	2 (2.1)	1 (1.0)
Nervous system disorders		
Tremor	3 (3.1)	0 (0.0)
Skin and subcutaneous tissue disorders		
Pruritus	2 (2.1)	0 (0.0)

Source: CSR 331-10-232, Section 14.1.1, CT-8.2.2.3

Treatment-emergent Adverse Events in Long-term, Open-label Trials

The most frequently reported TEAEs in the brexpiprazole group were schizophrenia, weight increased, insomnia, 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 (12.5% of completer's vs 8.5% of safety sample) than in the pooled population that included subjects who were treated for a shorter time period. Conversely, the incidence of subjects with schizophrenia was lower in the population of subjects who completed 52-weeks of treatment (2.9% of completer's vs 14.2% of safety sample) than in the pooled population that included subjects who were treated for a shorter time period.

Table 29: TEAEs Reported by At Least 5% of Subjects by SOC and PT (Safety Sample: Long-term, Open-label Trials - Schizophrenia)

System Organ Class MedDRA Preferred Term	BREX (N = 1426)	COMPLETERS (N = 681)
	n (%)	n (%)
Infections and Infestations		
Nasopharyngitis	92 (6.5)	62 (9.1)
Investigations		
Weight Increased	121 (8.5)	85 (12.5)
Nervous System Disorders		
Headache	103 (7.2)	62 (9.1)
Akathisia	81 (5.7)	38 (5.6)
Psychiatric Disorders		
Schizophrenia	203 (14.2)	20 (2.9)
Insomnia	118 (8.3)	55 (8.1)

Source: Module 5.3.5.3, SCS, Appendix 6, CT-LT-SZ-6.3

Treatment-emergent Adverse Events by Severity

In the **Short term controlled trials** severe TEAEs occurred in 6.6%, 5.4%, 8.6% and 6.6% of subjects in the brexpiprazole < 2 mg/ day, 2 to 4 mg/day, brexpiprazole >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 (3.2% vs 4.3%), agitation (0.7% vs 0.5%), psychotic disorder (0.3% vs 0.5%), and insomnia (0.3% vs 0.1% in the brexpiprazole 2 to 4 mg/day and placebo groups 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 [0.1%], in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively), psychomotor hyperactivity (2 subjects [0.2%] and 1 subject [0.1%], respectively), and rhabdomyolysis (2 subjects [0.2%] and 0 subjects, respectively).

In the 3 Phase 3 Fixed dose trials, the incidence of severe TEAEs was lower with higher doses (10.0%, 6.4%, 5.0%, and 4.6% in the brexpiprazole 0.25, 1 mg, 2, and 4 mg/day groups, respectively), and most groups had a lower incidence than in placebo (7.6%).

In the 3 Phase 3 Fixed dose trials, apart from severe TEAEs in the psychiatric disorders SOC (agitation, insomnia, psychotic disorders, schizophrenia), no severe TEAE by PT occurred in more than one subject.

In the Single-blind Stabilization phase of Trial 331-10-232 severe TEAEs occurred in 4.1% of subjects and in the Double-blind Maintenance phase severe TEAEs occurred in 2 [2.1%] brexpiprazole treated subjects (severe insomnia and decreased appetite) and 3 [2.9%] placebo treated subjects (severe psychotic disorder, suicidal ideation, and hypertension).

In the long-term open-label trials, severe TEAEs were reported in 7.4% of subjects. Most severe TEAEs were related to the underlying condition: schizophrenia (3.9%), psychotic disorder (0.6%), and agitation (0.4%). The only other severe TEAEs that occurred in more than 1 subject were weight increased (2 subjects, 0.1%), akathisia (2 subjects, 0.1%), suicidal ideation (2 subjects, 0.1%), and peritonitis (2 subjects, 0.1%, in one case fatal).

Treatment-emergent Adverse Events Potentially Related to Investigational Medicinal Product

In the short term controlled trials TEAEs potentially related to IMP occurred in 34.3%, 55,9% and 33% respectively in brexpiprazole 2-4 mg, brexpiprazole >4 mg and placebo treated subjects respectively. TEAEs potentially related to IMP occurred more frequently in the SOCs Nervous System Disorders, Psychiatric disorders and Gastrointestinal disorders. The most frequent TEAEs potentially related to IMP by PT, that occurred in brexpiprazole 2-4 mg treated patients more frequently than in PBO, with a difference form PBO >0.5%, were: akathisia (4.9% vs 3.6%), weight increased (3.3% vs 1.8%), tremor (2.3% vs 0.7%), sedation (1.7% vs 0.8%), extrapiramidal disorders (1.5% vs 0.8%) and dizziness (1.4% vs 0.8%).

In the fixed dose Phase 3 trials, a dose relationship was observed for TEAE assessed as potentially related to IMP (26.8%, 29.9%, 35.6%, of subjects in the brexpiprazole 1, 2, and 4 mg/day groups respectively, compared to 30.8% in placebo groups). These events were primarily in the Nervous System Disorders (11.1%, 15.4%, 19.3%, of subjects in the brexpiprazole 1, 2, and 4 mg/day groups respectively, compared to 13.4% in the placebo group), Psychiatric Disorders (8.5%, 8.9%, 10.7%of subjects in the brexpiprazole 1, 2, and 4 mg/day groups respectively, compared to 9.1% in placebo group), and Gastrointestinal Disorders (3.8%, 7.3%, 7.8%, and 7.9% of subjects in the brexpiprazole 1, 2, and 4 mg/day, and placebo groups, respectively) SOCs, and consisted of events such as headache, akathisia, insomnia, schizophrenia, agitation, constipation, nausea, dry mouth, and diarrhea.

In the 3 Phase 3 Fixed dose trials, among Potentially Drug Related TEAEs that occurred in at least 1% of subjects in the All Brexpiprazole Group and with a frequency higher than PBO, all TEAEs occurred more frequently in the brexpiprazole 4 mg group compared with lower doses (akathisia: 3.0%, 3.9%, 5.7%, and 3.9%; extrapyramidal disorders: 0.4%, 0.6%, 2.5% and 0.6%; sedation: 0.9%, 0.6%, 2.1% and 0.2%; dizziness: 0.9%, 0.6%, 1.9% and 0.6%; weight increased: 1.3%, 2.1%, 3.1% and 1.2%; blood creatinine phosphokinase increased: 1.3%, 0.6%, 1.5% and 0.6% in the brexpiprazole 1 mg, 2 mg, 4 mg, and placebo groups, respectively) apart from tremor and somnolence that occurred with similar frequency in the brexpiprazole 4 mg group compared with lower doses.

Treatment-emergent Adverse Events in Long-term Trials

In the Single-blind Stabilization 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%) SOCs. Akathisia (8.2%) and insomnia (5.8%) were the most frequently occurring potentially drug-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% vs 12.5%) and Psychiatric Disorders (4.1% vs 7.7%). Among TEAE assessed as potentially drug-related reported in at least 2% of subjects that occurred in the brexpiprazole group at a frequency higher than PBO was tremor (3.1% vs 0%).

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 37.1%. Weight increased (7.4%), akathisia (5.4%), insomnia (3.9%), schizophrenia (2.9%), headache (2.5%), somnolence (2.3%), tremor

(2.3%), extrapyramidal disorder (1.3%), dyskinesia (1.2%), and agitation (1.1%) were the most frequently reported (≥ 1% of subjects) TEAEs assessed as potentially related to IMP.

Treatment-emergent Adverse Events by Time of First Onset in long term open label trials
The time intervals used for analysis of the incidence of first onset of any TEAE in the long-term open lable trials were as follows:< 8 weeks (n = 1426); ≥ 8 weeks but < 14 weeks (n = 1118); ≥ 14 weeks but < 26 weeks
(n = 998); ≥26 weeks but < 52 weeks (n = 849); ≥ 52 weeks (n = 458).
The incidence of first onset of any TEAE was higher at < 8 weeks (43.5%) than at the subsequent time intervals (23.3%, 31.5%, 37.3%, and 11.6%, respectively).
In the Psychiatric disorders SOC, the following frequencies were observed by time intervals: 16.2%, 5.99%, 7.01%, 12.01%, 2.18% at onset time intervals < 8 weeks; ≥ 8 weeks but < 14 weeks; ≥ 14 weeks but < 26 weeks; ≥26 weeks but < 52 weeks, >52 weeks). The PT with the higher frequency of AE was schizophrenia, with the following frequencies observed by time intervals: 5.82%, 2.50%, 3.71%, 5.77%, 1.31% at onset time intervals < 8 weeks; ≥ 8 weeks but < 14 weeks; ≥ 14 weeks but < 26 weeks; ≥26 weeks but < 52 weeks, ≥52 weeks).
AEs of weight increased presented the following distribution by time interval: 1.96%, 2.24%, 3.31%, and 3.89% at onset time intervals < 8 weeks; ≥ 8 weeks but < 14 weeks; ≥ 14 weeks but < 26 weeks; ≥26 weeks but < 52 weeks). The frequency in the time interval ≥52 weeks was 0.66%. When patients were separated in groups according to prior treatment received, a higher frequency of reported events of weight increased with increasing exposure is most markedly seen in the prior brexpiprazole group, where reporting frequencies ranged from 1.82% to 6.17% for exposures of less than 8 weeks and 26 to 52 weeks, respectively.
In the time interval ≥52 weeks (n = 458) two events (0.4%) of tardive diskinesia occurred, compared to no events at earlier time intervals.
AEs of Electrocardiogram QT prolonged, presented the following distribution by time intervals: 3 events (0.21%) <8 weeks, 0 events >8->14 weeks, 1 event (0.10%) >14-<26 weeks, 3 events (0.35%) ≥26 weeks -< 52 weeks, 0 events ≥52 weeks.

AEs of Prolactin increased presented the following distribution by time intervals: 3 events (0.21%) <8 weeks, 1 event (0.09%) >8->14 weeks, 3 events (0.30%) >14-<26 weeks, 6 events (0.71%) ≥26 weeks -< 52 weeks, 0 events ≥52 weeks.

Safety topics of interest
Safety topics of interest were identified for additional analyses based on regulatory feedback, literature searches, and pharmacological class effects.

Table 30 Summary of Incidence for Selected Safety Topics of Interest (Safety Sample: Short-term, Controlled, Long-term, Controlled, and Long-term, Open-label Trials - Schizophrenia)

Topic	Percentage of Subjects						
	Short-term, controlled				Long-term, controlled[a]		Long-term, open-label
	BREX (N = 1748)	Placebo (N = 740)	ARI (N = 50)	QUET (N = 153)	BREX (N = 97)	Placebo (N = 104)	BREX (N = 1426)
Metabolic syndrome[b]	1.0	1.0	0.0	2.4	0.0	0.0	2.92
Any EPS event[c]	11.7	9.6	12.0	9.2	6.19	4.81	11.15
Akathisia	5.9	4.9	4.0	3.9	1.03	0.96	5.68
Dyskinetic	0.3	0.8	0.0	0.0	1.03	0.96	1.26
Dystonic	1.6	1.8	4.0	0.7	2.06	0.96	1.12
Parkinsonian-like	5.1	2.8	6.0	5.2	3.09	1.92	4.49
Residual events	0.2	0.1	0.0	0.7	--	--	--
Seizures	0.1	0.3	2.0	0.0	0.00	0.00	0.14
Somnolence	4.5	3.8	4.0	26.1	0.00	0.00	4.21
Suicidality TEAEs	0.5	0.4	0.0	0.0	0.00	1.92	1.61
Completed suicide	--	--	--	--	0.00	0.00	0.07
Intentional overdose	--	--	--	--	0.00	0.00	0.07
Intentional self-injury	0.1	0.0	0.0	0.0	0.00	0.00	0.14
Suicidal ideation	0.2	0.4	0.0	0.0	0.00	01.92	1.12
Suicide attempt	0.1	0.0	0.0	0.0	0.00	0.00	0.14
NMS	0.0	0.0	0.0	0.0	0.00	0.00	0.0
Hypersensitivity	1.8	0.8	2.0	1.3	1.03	1.92	1.19
VTEs	0.1	0.0	0.0	0.0	0.00	0.00	0.0

Note: Search criteria for TEAEs of interest (PTs) are presented in Appendix 5 of the SCS SAP (Module 5.3.5.3, SCS, Appendix 1).

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 postbaseline result (Ne is the denominator for the percentage calculation). For the treatment groups: Ne = 1417 (brexpiprazole), Ne = 608 (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 = 1131 (brexpiprazole) in long-term, open-label trials.

[c]EPS categories are presented as the overall incidence for each category (eg, akathisia = total akathisia events).

Source: Module 5.3.5.3, SCS; Appendix 4, CT-ST-SZ-7.5.1; CT-ST-SZ-7.6.1; CT-ST-SZ-7.7.1; CT-ST-SZ-7.9.1; CT-ST-SZ-7.10.1; CT-ST-SZ-7.13.1; CT-ST-SZ-7.16.1; and CT-ST-SZ-8.6.1; Appendix 5, CT-LC-SZ-7.5.1; CT-LC-SZ-7.6.1; CT-LC-SZ-7.7.1; CT-LC-SZ-7.9.1; CT-LC-SZ-7.10.2: CT-LC-SZ-7.13.1; CT-LC-SZ-7.16.1; CT-LC-SZ-8.6.1; and CT-LC-SZ-12.1.1; Appendix 6, CT-LT-SZ-7.5.1; CT-LT-SZ-7.6.1; CT-LT-SZ-7.7.1; CT-LT-SZ-7.9.1; CT-LT-SZ-7.10.1; CT-LT-SZ-7.13.1; CT-LT-SZ-8.6.1 and CT-LT-SZ-7.16.1.

Table 31 Summary of Incidence for Selected Safety Topics of Interest (Safety Sample: Short-term, Fixed-Dose Trials - Schizophrenia)

Table 5.2.4.16-1 Summary of Incidence for Selected Safety Topics of Interest (Safety Sample: Short-term, Fixed-Dose Trials - Schizophrenia)

Topic	Number and Percentage of Subjects				
	Brexpiprazole				Placebo
	0.25 mg (n = 90)	1 mg (n = 235)	2 mg (n = 482)	4 mg (n = 477)	(n = 484)
Increase in Body Weight ≥ 7%	4 (4.5)	17 (7.3)	44 (9.2)	40 (8.5)	16 (3.4)
Any EPS event	4 (4.4)	17 (7.2)	47 (9.8)	68 (14.3)	43 (9.9)
Akathisia	0 (0.0)	5 (4.2)	17 (4.6)	25 (6.9)	17 (4.6)
Psychomotor hyperactivity	0 (0.0)	1 (0.8)	2 (0.5)	1 (0.3)	1 (0.3)
Dyskinesia	1 (1.1)	0 (0.0)	1 (0.3)	2 (0.5)	1 (0.3)
Tardive dyskinesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Dystonia	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)	2 (0.5)
Muscle rigidity	0 (0.0)	1 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Muscle spasms	0 (0.0)	1 (0.8)	4 (1.1)	1 (0.3)	4 (1.1)
Bradykinesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Extrapyramidal disorder	1 (1.1)	0 (0.0)	4 (1.1)	8 (2.2)	6 (1.6)
Parkinsonism	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.8)	0 (0.0)
Tremor	2 (2.2)	2 (1.7)	9 (2.4)	10 (2.7)	2 (0.5)
Muscle twitching	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

Table 5.2.4.16-1 Summary of Incidence for Selected Safety Topics of Interest (Safety Sample: Short-term, Fixed-Dose Trials - Schizophrenia)

Topic	Number and Percentage of Subjects				
	Brexpiprazole				Placebo
	0.25 mg (n = 90)	1 mg (n = 235)	2 mg (n = 482)	4 mg (n = 477)	(n = 484)

Seizure TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)
Somnolence TEAEs	1 (1.1)	6 (2.6)	15 (3.1)	22 (4.6)	14 (2.9)
Suicidality TEAEs	0 (0.0)	4 (1.7)	1 (0.2)	2 (0.4)	3 (0.6)
Hypersensitivity TEAEs	2 (2.2)	4 (1.7)	8 (1.7)	8 (1.7)	2 (0.4)
VTE TEAEs	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

VTE: venous thromboembolism.
Note: Search criteria for TEAEs of interest (PTs) are presented in Appendix 5 of the SCS Statistical Analysis Plan (Module 5.3.5.3, SCS, Appendix 1). Subjects with multiple EPS TEAE were only counted once in total SOC row.
Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-6.9.1.4, CT-ST-SZ-7.6.3, CT-ST-SZ-7.9.3, CT-ST-SZ-7.10.3, CT-ST-SZ-7.13.3, CT-ST-SZ-7.16.3, and CT-ST-SZ-9.3.2.2.

Effect on glucose and on lipids were analysed in the following ways (besides being components of metabolic syndrome): 1) changes over time for metabolic parameters; 2) potentially clinically relevant changes (PCR) in metabolic parameters; 3) treatment-emergent shifts in glucose and lipids from normal at baseline to high at last visit; 4) TEAEs associated with glucose and lipids.

Hyperglycaemia and diabetes mellitus

In short term controlled trials, differences form placebo in the percentage of subjects meeting values of Potential Clinical Relevance for fasting glucose (>100 mg/dl) (37.5% vs 24.9%) and in the proportions of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) to high (8.8% vs 3.1% respectively) were observed only for the brexpiprazole >4 mg dose group.
However, in the maintenance phase of the long-term controlled trial 331-10-232, a higher frequency of patients treated with brexpiprazole (1-4 mg) experienced shifts in fasting glucose from normal to high (4.55%) and from normal or impaired (≥100 and <126 mg/dL) to high (3.8%), compared to PBO group (0 and 1.3%, respectively), and a slightly higher frequency of subjects met values of Potential Clinical Relevance in fasting glucose [20/89 (22.5%) in the brexpiprazole 1-4 mg , compared to 17/88 (19.3%) in the PBO group].
In long-term open-label trials, the percentages of subjects meeting Potential Clinical Relevance criteria for fasting glucose was higher (44.2%) and the percentages of subjects with shifts in fasting glucose from normal to high (6.1%) and from normal or impaired to high (16.94%) was higher than those seen in the short-term trials.
The TEAEs included in the search for effects of brexpiprazole treatment on glucose were based on the Standardised Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ]) narrow search for hyperglycemia plus terms from the broad list.
In short term controlled trials, the incidence of TEAEs related to blood glucose were reported by a similar proportion of subjects across treatment groups (0.4% brexpiprazole 2-4 mg vs 0.5% PBO). One serious TEAE of type 2 diabetes mellitus (from study 14644A, Patient) has been reported in 1 subject in the 2-4 mg dose group, in a who was diagnosed with moderate type II diabetes mellitus 20 days after the first dose of IMP. The event was considered by the investigator as related to IMP. BMI was obesewith no other relevant medical history. blood glucose was 5.9mmol/L at the Screening Visit; it increased during the study and was 6.7mmol/L at the Baseline Visit, 14.3mmol/L at Visit 6, and 17.7mmol/L at the Completion Visit. The HbA1c was 6.2% at the Screening Visit and 10% at the Completion Visit. Urine glucose was negative at both the Screening and Baseline Visits. However, it was 3+ at the Completion Visit. completed the study but the outcome of the event was not recovered.
In the Stabilization phase of trial 331-10-232, TEAEs related to metabolic parameters were diabetes mellitus (n = 1), hyperglycemia (n = 1), hypoglycemia (n = 1), and type 2 diabetes mellitus (n = 4).

None of these TEAEs were serious or resulted in discontinuation. In the Double-blind Maintenance phase, TEAEs related to blood glucose were reported by none of the subjects treated with brexpiprazole and by 1 subject in the placebo group.
In long term open label trials, treatment-emergent AEs related to blood glucose were reported by 22 subjects (1.5%) and 3 subjects (0.2%) were discontinued from IMP due to a TEAE related to blood glucose. The TEAEs reported by more than 1 subject were type 2 diabetes mellitus (9 subjects [0.6%]), blood glucose increased (5 subjects [0.4%]), 3 subjects each (0.2%) with hyperglycemia and diabetes mellitus, 2 subjects each (0.1%) with glycosylated hemoglobin increased and glucose tolerance impaired. All of the TEAEs related to blood glucose were considered to be not serious in the opinion of the investigator.

Ongoing Trials
In ongoing open-label MDD Trial 331-10-238, TEAEs of glycosylated haemoglobin increased and type 2 diabetes mellitus led to discontinuation of IMP for 3 subjects each; of these events leading to discontinuation, 1 event of type 2 diabetes mellitus was considered serious. Other TEAEs associated with glucose or lipid metabolism that led to discontinuation of IMP were reported in 1 subject each (PTs: blood glucose increased, blood triglycerides increased, and glucose tolerance impaired).

Dyslipidemia
In short term controlled trials and in the double blind maintenance phase of the long term trial 331-10-232 there were no relevant differences between brexpiprazole treatment groups and PBO in the percentage of subjects meeting Potential Clinical Relevance criteria for fasting lipids (total cholesterol fasting ≥240 mg/dl; LDL cholesterol fasting ≥160 mg/dl; HDL cholesterol fasting <40 mg/dl men and < 50 mg/ dl women; triglicerid fasting ≥150 mg/dl). However, in the long-term, open-label trials the percentages of subjects meeting Potential Clinical Relevance criteria for metabolic parameters were higher than those seen in the short-term trials.
In the fixed-dose trials treatment emergent shifts in fasting lipids from normal at baseline to borderline/high at last visit showed a higher frequency for the 4 mg dose group compared to PBO, for fasting total cholesterol [from <200 mg/ dl to ≥200: 23.9% vs 16.2%); fasting LDL (from <100 mg/ dl to ≥100: 38% vs 29.4%); for fasting triglycerides from normal (<150 mg/ dl) to high (200- <500) (8.3% vs 4.6%). One subject in the brexpiprazole 4 mg group presented shifts in fasting triglycerides from normal at baseline (<150 mg/ dl) to very high (≥500 mg/dl) at last visit, compared to no such events occurring in the PBO group or with lower brexpiprazole doses. In the overall "Short term controlled" safety sample, the incidences of treatment-emergent shifts for fasting LDL from normal (<100 mg/ dl) to borderline/ high (≥100) showed a higher frequency in brexpiprazole treated subjects compared to PBO (brexpiprazole 2-4 mg: 33.7%; >4 mg 34.3%; PBO: 31.1%).
A higher frequency was observed in the brexpiprazole >4 mg group compared to PBO in treatment-emergent shifts for fasting triglycerides from normal (<150 mg/ dl) to high (200- <500) (60%, 6/10; vs 36.4%, 36/99) and in treatment emergent significant changes in fasting HDL cholesterol from normal (≥40 mg/dl) to low (<40 mg/dl) (17.2%, 11/64 in the >4 mg brexpiprazole group; compared to 11.8%, 63/ 534 in PBO).
Treatment-emergent AEs related to lipids were reported by 8 (0.7%) subjects in the brexpiprazole 2 to 4 mg/day group and no subjects in the placebo group. One of the 8 subjects in the brexpiprazole 2 to 4 mg/day group with TEAEs also had a change that met the Potential Clinically Relevant criteria. One subject (, brexpiprazole 2 mg/day) was discontinued from IMP because of a TEAE related to lipids (blood triglycerides increased). All of the TEAEs related to lipids were considered to be not serious in the opinion of the investigator.

In the long term open label trials 13 subjects (0.91%) presented TEAEs associated with lipid parameters, with no event leading to discontinuation.

Emergence of Metabolic Syndrome

The percentage of subjects who developed metabolic syndrome (meeting ≥ 3 of the following criteria at a visit: central obesity [measured by waist circumference, ≥ 102 cm for males and ≥ 88 cm for females], dyslipidemia [triglycerides ≥ 150 mg/dL and/or HDL< 40 mg/dL for males and < 50 mg/dL for females cholesterol], hypertension [systolic BP ≥ 130 mmHg and Diastolic BP ≥ 85 mmHg] , and fasting glucose ≥ 110 mg/dL) was similar in the brexpiprazole and placebo groups in the short-term controlled trials (1.0% in both groups).

In the fixed-dose trials, the percentage of subjects with metabolic syndrome was 0.9% [9 subjects, 2 in 0.25 mg (2.8%), 5 in 2 mg (1.3%), and 2 in 4 mg/day (0.5%) groups] in the all brexpiprazole treatment group and 0.5% (2 subjects) in the placebo group

In the single blind Stabilization phase of study 331-10-232, a total of 10/384 subjects (2.6%) met criteria for metabolic syndrome. During the Double-blind Maintenance phase of the trial, no subjects in either treatment group developed metabolic syndrome (meeting 3 or more criteria at the same visit).

In the long term open label trials, a total of 33 subjects (2.9%) met 3 or more criteria for metabolic syndrome at the same visit in the long-term trials. Triglycerides ≥ 150 mg/dL was the most frequently met criterion (31.9%).

Body Weight

A weight increase that met the PCR criterion (increase of ≥7% from baseline in body weight) was observed in a higher percentage of subjects treated with brexpiprazole compared with placebo, both in short term controlled trials (9.1% in the brexpiprazole 2 to 4 mg/day group vs 3.8% PBO) and in the Double-blind Maintenance phase of the long term controlled trial 331-10-232 (5.2% vs 1.0%). At the end of the Stabilization phase of study 331-10-232 a ≥ 7% increase in body weight was reported for 25/202 subjects (12.4%).

The incidence of PCR weight increase (increase of ≥7% from baseline in body weight) in the fixed-dose trials showed a trend towards dose dependency (4.4%, 7.2%, 9.1% and 8.4% in the brexpiprazole 0.25 mg/day, 1 mg/day, 2 mg/day, and in the brexpiprazole 4 mg/day groups respectively, compared with 3.3% in the placebo group and 12% in the >4 mg group in short term trials.

In the long term open label trials, 20.7% of subjects had a weight increase that met the PCR criterion (increase of ≥7% from baseline in body weight). Overall, in the subjects who had a weight gain meeting the PCR criterion (weight gain ≥7%, 20.7% of subjects at any visit)-, weight increased over time, with mean weight gains of 7.0, 7.8, 9.0, 10.3, and 10.2 kg at Weeks 8, 14, 26, 38, and 52, respectively . .

No subjects in the short term controlled trials or in the maintenance trial 331-10-232 were discontinued from IMP due to a TEAE associated with weight increased) (BMI increased, obesity, waist circumference increased, weight gain, and weight increased.

Treatment-emergent Adverse Events Related to Extrapyramidal Symptoms
Fixed dose short term controlled trials
Table 32 : Summary of Incidence of TEAEs Associated with EPS (Safety Sample: Schizophrenia Fixed-dose Trials 331-10-230, 331-10-231, and 331-10-002)

EPS Category	Number (%) of Subjects				
	Brexpiprazole (mg/day)				Placebo (N = 484)
	0.25 mg (N = 90)	1 mg (N = 235)	2 mg (N = 482)	4 mg (N = 477)	
Any EPS TEAE	4 (4.4)	17 (7.2)	47 (9.8)	68 (14.3)	48 (9.9)
Akathisia events	0	8 (3.4)	24 (5.0)	34 (7.1)	27 (5.6)
Dyskinetic events	1 (1.1)	0	1 (0.2)	4 (0.8)	4 (0.8)
Dystonic events	0	4 (1.7)	6 (1.2)	9 (1.9)	8 (1.7)
Parkinsonian events	3 (3.3)	9 (3.8)	21 (4.4)	28 (5.9)	13 (2.7)
Residual events	0	0	0	1 (0.2)	0

Note: Subjects with multiple EPS TEAEs were only counted once in total EPS row.
Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-6.9.1.4.

akathisia events: include akathisia and psychomotor hyperactivity
parkinsonian events: includes bradikinesia, extrapiramidal disorder, hypertonia, parkinsonism, tremor

For most akathisia events –also in the PBO group- the time of first onset was in the category "study days 8-21" (4.45%, 2.86%, 0.92%, 0%, 2.71% in the brexpiprazole 4 mg/day, 2 mg/day, 1 mg/day, 0.25 mg/day and placebo groups respectively). The incidence of subjects taking at least 1 EPS medication during the trial increased with dose of brexpiprazole (2.2%, 6.7%, 8.2%, and 13.5% of subjects in the brexpiprazole 0.25, 1, 2, and 4 mg/day groups, respectively). The incidence in the placebo group was 7.3%.

Short term controlled trials
In the pool "short term controlled trials", the percentage of subjects who reported TEAEs associated with EPS was 12.0% in the brexpiprazole 2 to 4 mg/day group compared with 9.6% in the placebo group. Akathisia was the most frequently reported EPS TEAE in the brexpiprazole 2 to 4 mg/day group (5.6%), followed by tremor (2.7%), included in the category parkinsonian events.
No subjects in any treatment group had a serious TEAE of EPS.
Most TEAEs associated with EPS were mild or moderate in severity. Four subjects (0.2%) in the all brexpiprazole treatment group had TEAEs associated with EPS that were considered to be severe (myoclonus 0.25 mg, dose not changed, recovered/ resolved-, 2 cases psychomotor hyperactivity: 2-4 mg, drug withdrawn, recovered/resolved-; 4 mg, drug withdrawn, recovered/ resolved- akathisia: 5 mg±1 mg, dose not changed, not resolved) and 1 subject (0.1%) in the placebo group had psychomotor hyperactivity.
Eight subjects (0.4%) in the all brexpiprazole treatment group were discontinued from IMP due to a TEAE associated with EPS: two subjects receiving brexpiprazole 5 mg±1 mg, 4 subjects receiving brexpiprazole 4 mg (2 psychomotor hyperactivity, tremor, extrapyramidal disorders), and 2 subjects receiving brexpiprazole 2-4 mg (tremor, psychomotor hyperactivity). Two subjects in the placebo group discontinued from IMP because of EPS (extrapyramidal disorder and psychomotor hyperactivity).
In short-term controlled Trials 331-07-203, 331-10-230, and 331-10-231, a total of 88 subjects (10.7%) in the brexpiprazole 2 to 4 mg/day group took a medication for EPS during the trial, compared with 36 subjects (7.8%) in the placebo group.

Short term active controlled study 14644A
In the quetiapine arm of study 14644A the frequency of patients with EPS related to TEAEs was 9.2% (n=14), similar to the frequency in the brexpiprazole arm (10.7%, n= 14), and higher compared to PBO (6.2%, n=6.2%). Akathisia was the most frequently reported EPS TEAE in the brexpiprazole group (6.0%, compared to 3.9% in quetiapine treated patients and 3.1% in PBO) followed by tremor (3.3%, compared to 4.6% in quetiapine treated patients and 6.6% in PBO).

Short term active controlled study 331-07-203
In the aripiprazole 15 ± 5 mg arm of study 331-07-203 the frequency of patients with EPS related to TEAEs was 12% (n = 6), similar to the frequency in the placebo arm (13.7%, n= 13), compared to 24.7% (n = 23), 14.4% (n = 13),15.7% (n = 14) and 7.1% (n=3) in the brexpiprazole groups 5.0 ± 1mg, 2.5 ± 0.5 mg, 1.0 ± 0.5 mg, 0.25 mg respectively. Akathisia was reported as EPS TEAE in the brexpiprazole groups (2.4% in the 0.25 mg dose group, 6.7% in the 1 ± 0.5 mg dose group, 5.6% in the 2.5 ± 0.5 mg dose group, 15.1% in the 5 ± 1mg dose group compared to 4.0% in aripiprazole treated patients and 4.2% in PBO).

Long-term trials
In the double-blind maintenance phase of long-term trial 331-10-32, at least one TEAEs related to EPS occurred in 6.19% (6/97) and 4.81% (5/104) of subjects in the brexpiprazole and placebo treatment groups respectively.
In long-term open label trials 11% (159/1426) of subjects experienced TEAE associated with EPS. In five of these subjects the events were serious (resulted in hospitalization) and led to discontinuation (4 subjects) or dose reduction (1 subject). In the long-term open label trials there were two events of tardive dyskinesia. The incidence of EPS-related TEAE in the long-term, open-label trials by prior treatment in the parental trial showed a higher frequency in the prior placebo (12.6%) and de novo groups (14.5%), compared with the prior brexpiprazole group (9.1%).

All Clinical Pharmacology Trials Group
Treatment-emergent AEs associated with EPS leading to discontinuation of IMP (PTs: akathisia, dystonia, and extrapyramidal disorder) were reported for a total of 10 subjects in the Clinical Pharmacology Trials group in the brexpiprazole-treated subjects (n = 877) as follows: extrapyramidal disorder (5/877 subjects [0.6%], including 3 subjects with schizophrenia and 2 subjects with MDD), akathisia (4/877 subjects [0.5%], including 2 healthy subjects and 2 subjects with schizophrenia), and dystonia (1/877 subjects [0.1%], 1 subject with schizophrenia). There were no EPS-related events in placebo-treated subjects (n = 105).
One EPS-related event (extrapyramidal syndrome) considered serious, severe in intensity, possibly related to the study medication and leading to discontinuation of IMP occurred in one MDD subject 8 days after randomization to brexpiprazole 4 mg. The subject had no reported medical history. Concomitant medication taken at the time of the event included escitalopram oxalate and propanolol.

Analyses of Extrapyramidal Symptoms Scale Evaluations

Changes from Baseline in EPS Evaluations
In short term controlled trials, the mean scores at baseline for the SAS, BARS, and AIMS were similar across groups. For all 3 evaluations, the mean changes from baseline to last visit were small and similar in the all brexpiprazole and placebo groups. Similar results were seen for analyses using the fixed-dose trials; no meaningful differences were seen among the 4 dose groups of brexpiprazole.

In the Long-term, Controlled Trial 331-10-232, symptoms of akathisia, involuntary movement, or tremor at baseline were very infrequent in both treatment groups based on mean baseline scores for the SAS, BARS, and AIMS evaluations (all mean scores ≤ 0.5).

Long-term, Open-label Trials
For all 3 EPS scale evaluations, the mean change from baseline was small and there was minimal variation during the course of the long-term trials.

Treatment-emergent Shifts in EPS Evaluation Scores
In short term controlled trials, treatment-emergent akathisia, based on on-treatment shifts from baseline in BARS Global Score from ≤ 2 to > 2, was observed in 1.3% (16 subjects) and 1.1% (8 subjects) of subjects in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively.
Treatment-emergent Parkinsonism, based on on-treatment shifts from baseline in SAS Total Score from ≤ 3 to > 3, was observed in 7.1% (68 subjects) and 4.8% (29 subjects) in the brexpiprazole 2 to 4 mg/day and placebo groups, respectively. Treatment emergent shifts from baseline in AIMS Total Score from ≤1 to ≥2, were observed in 47/1188 subjects (4.0%) in brexpiprazole 2-4 mg and 36/728 (4.9%) in placebo group.
Available data from fixed dose trials showed a trend towards a higher frequency of PCR shifts in BARS with higher brexpiprazole doses (0.9%, 0.8% and 2.1% in the 1 mg group, 2 mg group and 4 mg group respectively, compared with 1.0% in the placebo group), SAS (5.9%, 5.9% and 7.8% in the 1 mg, 2 mg and 4 mg groups, respectively compared with 5.3% with PBO) , or AIMS (2.6%, 3.8% and 4.0% in the 1 mg group, 2 mg group, and 4 mg group, respectively, compared with 4.6% with PBO).

Long-term, Controlled Trial 331-10-232
The mean changes from baseline to last visit were small (< 0.2) for all of the EPS evaluation scales, and similar between the brexpiprazole and placebo groups. Treatment-emergent akathisia, based on on-treatment shifts from baseline in BARS Global Score from ≤ 2 to > 2, was observed in 1 subject each (1.0%) in the brexpiprazole (1/96) and placebo group (1/104). No brexpiprazole-treated subjects with on-treatment shifts from baseline in BARS Global Score had a serious TEAE or discontinued because of a TEAE of akathisia.
Treatment-emergent Parkinsonism, based on on-treatment shifts from baseline in SAS Total Score from ≤ 3 to > 3, was observed in 2/96 (2.1%) and 4/104 (3.9%) subjects in the brexpiprazole and placebo groups, respectively. Of the subjects with shifts, parkinsonism was not a serious TEAE nor did it lead to discontinuation of IMP.Treatment emergent shifts from baseline in AIMS Total Score from ≤1 to ≥2, were observed in 6/96 subjects (6.25%) in brexpiprazole and 10/104 (9.62%) in placebo group.

Long-term, Open-label Trials
Treatment-emergent akathisia, based on on-treatment shifts from baseline in BARS Global Score from ≤ 2 to > 2, was observed in 28/1411 subjects (2.0%). The majority of these shifts were a 1-time occurrence. Akathisia led to discontinuation of IMP in four subjects with shifts. Treatment-emergent Parkinsonism, based on on-treatment shifts from baseline in SAS Total Score from ≤3 to > 3, was observed in 70/1129 subjects (6.20%). No subject with shifts had a Parkinsonism TEAE that led to discontinuation of IMP. Treatment emergent shifts from baseline in AIMS Total Score from ≤1 to ≥2, was observed in 91/1411 subjects (6.45%).

Agranulocytosis, Neutropenia, and Leukopenia
In short term controlled trials, a similar proportion of subjects experienced these TEAEs between brexpiprazole and PBO treated subjects (0.2 vs 0.4%), no such events occurred during the double blind

maintenance phase of trial 331-10-232, and 6 subjects (0.42%) in the Long-term open label trials experienced TEAEs of hematopoietic/leucopenia events.
In the brexpiprazole < 2 mg/day group, 1 subject (0.2%) had a TEAE of agranulocytosis. The agranulocytosis was reported as a TEAE based on a single occurrence of a low (PCR) percentage of neutrophils (9.8%) on Day 22. On Day 8, the neutrophil percentage was within the reference (45.9%). The dose of IMP was not changed in response to the TEAE. On Day 30, the neutrophil percentage was within normal range (50.2%).
Two (2.1%) subjects in the brexpiprazole group had PCR values for WBC (one case of decrease ≤2800 and one case of increase >16.000), compared with 0 (0.0%) subjects in the placebo group.

Ongoing Trials
In ongoing blinded trials, TEAEs related to haematopoietic effects/leukopenia resulted in discontinuation of one subject and one was considered to be serious as of the cutoff date. In ongoing double-blind, placebo-controlled MDD Trial 331-12-282, 1 subject experienced a TEAE of differential WBC count abnormal which led to discontinuation of IMP. In ongoing, open-label MDD Trial 331-10-238, 1 subject had a serious TEAE of iron deficiency anemia.

Neuroleptic Malignant Syndrome
There were no subjects in the short-term, controlled trials, in any treatment group during the Stabilization 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. A search conducted in the Applicant's safety database for postmarketing events of the PT 'neuroleptic malignant syndrome' reported with brexpiprazole cumulatively through 25 Jun 2017 retrieved 9 reported events of NMS in the postmarketing setting. Even though the limited available data do not allow to definitely conclude on the causal association with brexpiprazole in these specific cases (either due to little or no detail regarding time to onset, little information regarding concomitant medications, possible cofounders in medical history or concomitant medications or in some cases not clearly described events of NMS), a causal relationship is suspected due to the known association between NMS with administration of antipsychotics.

Orthostatic Hypotension, Dizziness and Syncope
In short term controlled trials, potentially clinically relevant changes in orthostatic hypotension (≥20 mmHg decrease in systolic blood pressure and ≥25 beats per minute increase in heart rate from supine to sitting/ standing) were observed in 1.6% in brexpiprazole 2-4 mg treated patients compared to 2.3% in placebo. In the Long term, Controlled Trial 331 10 232, there were no TEAEs of orthostatic hypotension reported in any treatment group during the Double blind Maintenance phase. During the Stabilization phase a PCR value of orthostatic hypotension was reported in 4 subjects. In long term open label trials 15 subjects (1.1%) met PCR criteria for orthostatic hypotension.
In short term controlled trials, TEAEs of dizziness, syncope or orthostatic hypotension occurred in 2.8% of subjects in the brexpiprazole 2-4 mg/ day group compared with 1.5% in the placebo group. Dizziness was the most frequently reported TEAE of this set of events in all groups.
Two subjects had severe events that led to discontinuation of IMP: one serious event of dizziness (brexpiprazole 2 to 4 mg/day group) and one event of syncope (brexpiprazole > 4 mg/day group).

Table 33 Incidence of TEAEs - Events Related to Orthostatic Hypotension, Dizziness, and Syncope (Safety Sample: Short term, Controlled Trials - Schizophrenia)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects						
	Brexpiprazole				Placebo	ARI	QUET
	< 2 mg (n = 456)	2 - 4 mg (n = 1199)	> 4 mg (n = 93)	ALL (n = 1748)	(n = 740)	(n = 50)	(n = 153)
Subjects With Any Treatment Emergent Adverse Events Related to Orthostatic Hypotension, Dizziness, and Syncope	8 (1.8)	34 (2.8)	8 (8.6)	50 (2.9)	11 (1.5)	1 (2.0)	22 (14.4)
Nervous System Disorders							
Dizziness	8 (1.8)	28 (2.3)	5 (5.4)	41 (2.3)	10 (1.4)	1 (2.0)	18 (11.8)
Dizziness Postural	0 (0.0)	3 (0.3)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.7)
Vascular Disorders							
Orthostatic Hypotension	0 (0.0)	4 (0.3)	2 (2.2)	6 (0.3)	1 (0.1)	0 (0.0)	4 (2.6)

Of the set of topics being analyzed; a subject may have reported more than 1 TEAE that was grouped under the same topic
of interest.
Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-7.12.1.

The incidence of TEAEs for orthostatic hypotension, dizziness, and syncope in the fixed-dose trials was 2.2% (2 subjects), 0.9% (2 subjects), 2.1% (10 subjects), 3.1% (15 subjects) in the brexpiprazole 0.25 mg, 1 mg, 2 mg, and 4 mg/day groups, respectively, compared with 1.4% (7 subjects) in the placebo group.
In the double blind maintenance phase of study 331-10-232, there were no TEAEs of orthostatic hypotension, dizziness and syncope in the brexpiprazole group.
In long term open-label trials, the percentage of subjects who reported a TEAE of dizziness, dizziness postural, presyncope, syncope, or orthostatic hypotension was 2.0%.

Hyperprolactinaemia
Potentially clinically relevant prolactin values (> 1 × upper limit of normal [ULN]) were evaluated, along with changes from baseline and prolactin-related TEAEs.

Potentially Clinically Relevant Changes in Prolactin
Short-term, Controlled Trials
All subjects with a prolactin value > 3 × ULN met that criterion at 1 visit only.

Table 34 Values of Potential Clinical Relevance - Prolactin (Safety Sample: Short-term, Controlled Trials - Schizophrenia)

Prolactin (ng/mL)	Number (%) of Subjects with On-Treatment Result Meeting Criterion						
	Brexpiprazole				Placebo	ARI	QUET
	< 2 mg	2 - 4 mg	> 4 mg	All			
Females							
> 1 x ULN	24/181 (13.3)	64/466 (13.7)	7/37 (18.9)	95/684 (13.9)	19/295 (6.4)	0/16 (0.0)	5/61 (8.2)

Prolactin (ng/mL)	Number (%) of Subjects with On-Treatment Result Meeting Criterion						
	Brexpiprazole				Placebo	ARI	QUET
	< 2 mg	2 - 4 mg	> 4 mg	All			
> 2 x ULN	4/181 (2.2)	18/466 (3.9)	1/37 (2.7)	23/684 (3.4)	12/295 (4.1)	0/16 (0.0)	0/61 (0.0)
> 3 x ULN	2/181 (1.1)	7/466 (1.5)	1/37 (2.7)	10/684 (1.5)	3/295 (1.0)	0/16 (0.0)	1/61 (1.6)
Males							
> 1 x ULN	14/259 (5.4)	76/684 (11.1)	0/55 (0.0)	90/998 (9.0)	41/399 (10.3)	0/34 (0.0)	11/82 (13.4)
> 2 x ULN	5/259 (1.9)	10/684 (1.5)	0/55 (0.0)	15/998 (1.5)	13/399 (3.3)	0/34 (0.0)	1/82 (1.2)
> 3 x ULN	2/259 (0.8)	7/684 (1.0)	0/55 (0.0)	9/998 (0.9)	9/399 (2.3)	0/34 (0.0)	2/82 (2.4)

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-8.3.1.

The incidence of PCR prolactin elevations at > 1 × ULN in the fixed-dose trials for female subjects was higher in the brexpiprazole 0.25 mg/day and 4 mg/day groups (18.5%, and 15.3%, respectively) compared with the 1 mg/day and 2 mg/day dose groups (12.4% and 12.1%, respectively). A total of 20 female subjects, in the brexpiprazole 1 mg/day, 2 mg/day, and 4 mg/day dose groups, had an elevation > 2 × ULN. Five female subjects (2 subjects each in the 2 mg/day and 4 mg/day dose groups, and 1 subject in the 1 mg/day dose group) had an elevation > 3 × ULN at 1 visit only. Three female subjects (1 subject in the 2 mg/day dose group and 2 subjects in the 4 mg day dose group) had an elevation > 3 x ULN at more than one visit. Data were similar for male subjects. Five of 8 brexpiprazole-treated male subjects with elevations > 3 × ULN were in the brexpiprazole 4 mg/day group. Elevations were reported for 7 of the 8 subjects at 1 visit only and were asymptomatic.
The frequencies of shifts from baseline with potential clinical relevance of increase for prolactin in patients with normal prolactin values at baseline, as well as mean and median changes from baseline, showed a trend towards a dose-dependency in females patients, in fixed dose trials (> 1 x ULN during treatment in females with normal prolactin at baseline were observed in 16.4%, 15.2% and 20.4% in females treated with brexpiprazole 1 mg, 2 mg and 4 mg, respectively, compared to 9.8% in PBO. Increases >2 x ULN were observed in 3.0%, 5.8% and 1.4% in females treated with brexpiprazole 1 mg, 2 mg and 4 mg, respectively, compared to 3.8% in PBO. Increases > 3 x ULN occurred only in subjects treated with the higher 4 mg brexpiprazole dose (3/144, 2.1% in females, compared with 0 in PBO).
In males smaller changes were observed, with smaller differences from placebo.
From available data, frequencies of prolactin increases from baseline PCR in females patients with normal prolactin at baseline tended to be higher in long term uncontrolled trials compared to those observed in short term trials (long term uncontrolled trials: females: >1 x ULN: 24.2%, >2 x ULN: 3.9%, >3 x ULN: 2.9%; males: >1 x ULN: 17.1%, >2 x ULN: 2.7%, >3 x ULN: 0.5% vs short term controlled trials: females: >1 x ULN: 17.8%, >2 x ULN: 2.9%, >3 x ULN: 0.9%; males: >1 x ULN: 16.1%, >2 x ULN: 1.1%, >3 x ULN: 0.4%).

Long-term, Controlled Trial 331-10-232

Table 35 Values of Potential Clinical Relevance – Prolactin in the Double-blind Maintenance Phase of Trial 331-10-232 (Safety Sample)

Prolactin (ng/mL)	Number (%) of Subjects with On-Treatment Result Meeting Criterion	
	Brexpiprazole	Placebo
Females		
> 1 × ULN	2/38 (5.26)	1/38 (2.63)

Prolactin (ng/mL)	Number (%) of Subjects with On-Treatment Result Meeting Criterion	
	Brexpiprazole	**Placebo**
> 2 × ULN	2/38 (5.26)	1/38 (2.63)
> 3 × ULN	0/38 (0.00)	2/38 (5.26)
Males		
> 1 × ULN	2/55 (3.64)	3/61 (4.92)
> 2 × ULN	0/55 (0.00)	3/61 (4.92)
> 3 × ULN	0/55 (0.00)	2/61 (3.28)

Source: Module 5.3.5.3, Appendix 5, CT-LC-SZ-8.3.1.

The majority of subjects in the Double-blind Maintenance phase were male; 116 male and 76 female subjects were assessed for prolactin.

Long-term, Open-label Trials

Values of PCR for prolactin (> 1 × ULN) were observed in 98 female subjects (19.8%) and 87 male subjects (12.9%); the incidences in the short-term trials were 13.9% and 9.0%, respectively. There were 19 female subjects (3.8%) and 27 male subjects (4.0%) with a value > 2 ×ULN. There were 15 female subjects (3.0%) and 14 male subjects (2.1%) with a value > 3 × ULN. Of these 29 subjects with a prolactin value > 3 × ULN, 23 met that criterion at only 1 assessment. None of these subjects reported a reproductive system symptom.

Treatment-emergent Adverse Events Associated with Prolactin

To assess for clinical significance, a search was conducted in subjects with a prolactin elevation > 1 × ULN using the following PTs: blood prolactin increased, blood prolactin abnormal, hyperprolactinemia, galactorrhea gynaecomastia, breast swelling, breast enlargement, breast mass, breast tenderness, amenorrhea, oligomenorrhea, anovulatory cycle, hypomenorrhea.

Short-term, Controlled Trials

Treatment-emergent AEs related to prolactin (blood prolactin increased, blood prolactin decreased, or hyperprolactinemia) were reported in 22 subjects (1.3%) in the brexpiprazole-treated groups (subjects were in the 2 to 4 mg dose group [n = 17; 1.4%], < 2 mg dose group [n = 3; 0.7%], > 4 mg dose group [n = 2; 2.2%]) and 8 subjects (1.1%) in the placebo group. All of these TEAEs were considered mild or moderate in severity by the investigator. The dose of IMP was not changed for any of these subjects due to the increase in prolactin. Five of these subjects had a prolactin level > 3 × ULN. In the fixed-dose trials, blood prolactin increased was observed in 10 subjects (2.1%) in the brexpiprazole 4 mg/day group, 6 subjects (1.2%) in the brexpiprazole 2 mg/day group, 3 subjects (1.3%), in the brexpiprazole 1 mg/day group, 7 subjects (1.4%) in the placebo group, and by no subjects in the brexpiprazole 0.25 mg/day group. Hyperprolactinemia was reported in 2 subjects each in the brexpiprazole 1 mg/day (0.9%), brexpiprazole 2 mg/day (0.4%), and placebo groups (0.4%), and by 1 subject (0.2%) in the brexpiprazole 4 mg/day group. No subjects reported hyperprolactinemia in the brexpiprazole 0.25 mg/day group.

A search of the clinical database for TEAEs in the SOCs of Reproductive System and Breast Disorders and Psychiatric Disorders (sexual function-related AEs; eg, decreased libido, anorgasmia) for the 22 subjects with TEAEs related to prolactin revealed that they had none of these types of TEAEs in these SOCs.

In short term controlled trials among subjects with potentially clinically relevant changes (PCR) in prolactin (> 1 × ULN), one patients each in brexpiprazole and PBO group experienced dysmenorrea and no subjects experienced sexual function related TEAEs.

Long-term, Controlled Trial 331-10-232
No TEAE meeting the criteria for prolactin have been reported in Trial 331-10-232.

Long-term, Open-label Trials
Treatment-emergent AEs related to prolactin (blood prolactin increased, blood prolactin abnormal, hyperprolactinemia, galactorrhea gynaecomastia, breast swelling, breast enlargement, breast mass, breast tenderness, amenorrhea, oligomenorrhea, anovulatory cycle, hypomenorrhea) were reported in 23 subjects (1.6%); 7 male subjects (3 with blood prolactin increased and 4 with hyperprolactinemia) and 16 female subjects (11 with blood prolactin increased and 5 with hyperprolactinemia). The dose was reduced in 4 female subjects due to the increase in prolactin, but no subject was discontinued due to the increase. Two of these 23 subjects had an elevation of > 3 × ULN. A search of the clinical database for TEAEs in the SOCs of Reproductive System and Breast Disorders and Psychiatric Disorders (sexual function-related AEs; eg, decreased libido, anorgasmia) for the 23 subjects with TEAEs related to prolactin revealed none had these types of TEAEs in these SOCs.
In long term trials among subjects with potentially clinically relevant changes (PCR) in prolactin (> 1 × ULN) one patient presented a TEAE of menstruation irregular and one patient presented a TEAE of libido decreased. The event was mild in severity and was considered possibly related to the study drug.

QT Prolongation

Short term controlled trials
Table 2 Number (%) of Subjects with Categorical Changes in QTcB or QTcF of Potential Clinical Relevance (Safety Sample: Short-term, Controlled Trials - Schizophrenia)

EGTEST	Category	Number (%) of Subjects						
		Brexpiprazole				Placebo	ARI	QUET
		< 2 mg (n = 439)	2 - 4 mg (n = 1160)	> 4 mg (n = 92)	All (n = 1691)	(n = 707)	(n = 50)	(n = 153)
QTCB	INCREASE > 30 - ≤ 60 MSEC	60 (13.7)	129 (11.1)	8 (8.7)	197 (11.6)	87 (12.3)	3 (6.0)	39 (25.5)
	INCREASE > 60 MSEC	1 (0.2)	9 (0.8)	1 (1.1)	11 (0.7)	9 (1.3)	0 (0.0)	7 (4.6)
	NEW ONSET (> 500 MSEC)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
QTCF	INCREASE > 30 - ≤ 60 MSEC	28 (6.4)	66 (5.7)	6 (6.5)	100 (5.9)	45 (6.4)	1 (2.0)	13 (8.5)
	INCREASE > 60 MSEC	0 (0.0)	3 (0.3)	1 (1.1)	4 (0.2)	1 (0.1)	0 (0.0)	1 (0.7)
	NEW ONSET (> 500 MSEC)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-10.3.1.

Table 37 Number (%) of Subjects with Categorical Changes in QTcB or QTcF of Potential Clinical Relevance (Safety Sample: Short- term, Fixed-dose, Controlled Trials - Schizophrenia)

EGTEST	Category	Number (%) of Subjects

		Brexpiprazole					Placebo
		0.25 mg (n = 85)	**1 mg (n = 226)**	**2 mg (n = 467)**	**4 mg (n = 453)**	**All (n = 1231)**	**(n = 455)**
QTcB	Increase > 30 to ≤ 60 msec	12 (14.1)	34 (15.0)	57 (12.2)	40 (8.8)	143 (11.6)	56 (12.3)
	Increase > 60 msec	1 (1.2)	0 (0.0)	3 (0.6)	3 (0.7)	7 (0.6)	3 (0.7)
	New onset (> 500 msec)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
QTcF	Increase > 30 to ≤ 60 msec	8 (9.4)	15 (6.6)	27 (5.8)	21 (4.6)	71 (5.8)	29 (6.4)
	Increase > 60 msec	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.2)
	New onset (> 500 msec)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Trials: 331-10-230, 331-10-231, and 331-10-002

Source: Appendix 3, MAAD80-R78.1.

Maintenance phase of the long term controlled trial 331-10-232

Table 38 Number (%) of Subjects with Categorical Changes in QTcB or QTcF of Potential Clinical Relevance in the Double-blind Maintenance Phase of Trial 331-10-232 (Safety Sample)

EGTEST	**Category**	**Number (%) of Subjects**	
		Brexpiprazole	**Placebo**
		(n = 95)	**(n = 100)**
QTCB	INCREASE > 30 ≤ 60 MSEC	9 (9.47)	13 (13.00)
	INCREASE > 60 MSEC	3 (3.16)	1 (1.00)
	NEW ONSET (> 500 MSEC)	0 (0.00)	0 (0.00)
QTCF	INCREASE > 30 ≤ 60 MSEC	8 (8.42)	8 (8.00)
	INCREASE > 60 MSEC	0 (0.00)	0 (0.00)
	NEW ONSET (> 500 MSEC)	0 (0.00)	0 (0.00)

Source: Module 5.3.5.3, SCS, Appendix 5, CT-LC-SZ-10.3.1.

Long term open-label trials,

Table 3 Number (%) of Subjects with Categorical Changes in QTcB or QTcF of Potential Clinical Relevance (Safety Sample: Long-term, Open-label Trials - Schizophrenia)

EGTEST	**Category**	**Number (%) of Subjects**
		Brexpiprazole
		(n = 1380)
QTCB	INCREASE > 30 - ≤ 60 MSEC	254 (18.41)
	INCREASE > 60 MSEC	22 (1.59)
	NEW ONSET (> 500 MSEC)	1 (0.07)

EGTEST	Category	Number (%) of Subjects
		Brexpiprazole
		(n = 1380)
QTCF	INCREASE > 30 - ≤ 60 MSEC	138 (10.00)
	INCREASE > 60 MSEC	5 (0.36)
	NEW ONSET (> 500 MSEC)	1 (0.07)

Source:Module 5.3.5.3, SCS, Appendix 6, CT-LT-SZ-10.3.1.

A total of 7 subjects (0.5%) had a TEAE related to QT prolongation. There were 8 TEAEs of ECG QT prolonged in 7 subjects. All were considered related to IMP, were mild or moderate in severity, and were not serious TEAEs. Two subjects were withdrawn from IMP.

Potentially Clinically Relevant ECG Changes

Short-term, Controlled Trials

The most frequently reported PCR changes overall were ST/T morphological changes, including myocardial ischemia, symmetrical T-wave inversions, and increases in QTcF ≥ 450 msec, which were reported in a comparable proportion of subjects in the brexpiprazole 2 to 4 mg/day, all brexpiprazole, and placebo groups. In short-term, Controlled Trials, increases in QTcF ≥ 450 msec occurred in 9/439 (2.1%), 28/1156 (2.4%), 4/91 (4.4%) and 20/699 (2.9%) subjects, in subjects receiving brexpiprazole <2 mg, 2-4 mg, >4 mg and placebo respectively.

In fixed dose trials, increases in QTcF ≥ 450 msec were observed in 2/85 (2.4%), 6/226 (2.7%), 11/466 (2.4%) and 8/453 (1.8%) and 10/452 (2.2%) subjects, in subjects receiving brexpiprazole 0.25 mg, 1 mg, 2 mg, 4 mg and placebo respectively.

Long-term, Controlled Trial 331-10-232
Table 40 Incidence of Potentially Cninically Relevant Electrodiagram Abnormalities (Double-blind Maintenance Phase, Safety Sample)

Table 12.5.3.2-1 Incidence of Potentially Clinically Relevant Electrocardiogram Abnormalities (Double-blind Maintenance Phase, Safety Sample)				
Type Abnormality	Brexpiprazole (1 to 4 mg)		Placebo	
	N[a]	n[b] (%)	N[a]	n[b] (%)
Rhythm				
Supraventricular premature beat	95	1 (1.1)	101	1 (1.0)
Ventricular premature beat	95	2 (2.1)	101	2 (2.0)
Conduction				
Right bundle-branch block	95	0 (0.0)	101	2 (2.0)
ST/T Morphological				
Symmetrical T-wave inversion	95	5 (5.3)	101	5 (5.0)
Increase in QTcF	95	2 (2.1)	100	3 (3.0)

Note: Tests were included only if they had criteria for ECG test values that were PCR (CT-12.1).
[a] N is the total number of subjects with at least 1 postbaseline numeric result for the given ECG parameter.
[b] n is the number of subjects with a PCR ECG value; the denominator for percentage calculation is N.
Source: CT-12.4.1.

Long-term, Open-label Trials
The most commonly reported PCR changes overall were ST/T morphology abnormalities: myocardial ischemia in 18 (1.3%) subjects, symmetrical T-wave inversions in 58 (4.2%) subjects, and increase in QTcF ≥ 450 msec in 66 (4.8%) subjects. In addition, the heart rhythm disorders sinus bradycardia, supraventricular premature beat, and ventricular premature beat were reported by 34 (3.1%), 39 (2.8%), and 26 (1.9%) subjects, respectively.

All Clinical Pharmacology Trials Group
There were 2 events of potential interest related to ECG or cardiac abnormalities in clinical pharmacology trials; both led to discontinuation of IMP. An elderly subject with MDD (Subject, treated with brexpiprazole) was discontinued from IMP due to a TEAE of electrocardiogram QT prolonged that was assessed as related to IMP. A healthy subject (Subject, treated with brexpiprazole) was discontinued from IMP due to TEAEs of chest discomfort and chest pain; the cardiac assessments (enzymes, ECGs) were negative, the etiology was undetermined, and both events were assessed as unlikely related to the IMP.

Ongoing Trials
In ongoing, double-blind agitation associated with dementia of Alzheimer's type Trial 331-12-283, two –still blinded- subjects were discontinued from IMP due to nonserious TEAEs of electrocardiogram QT prolonged.
In ongoing, open-label MDD Trial 331-10-238, 3 events of electrocardiogram QT prolonged have been reported that resulted in discontinuation from the trial, 1 of which was a serious TEAE.

Change from Baseline - Electrocardiogram Results

Short-term, Controlled Trials

Mean baseline ECG parameters were similar among treatment groups. Mean changes from baseline at last visit were small in magnitude and similar across groups. For QTcF, there was a small increase in the brexpiprazole < 2 mg, brexpiprazole 2 to 4 mg, all brexpiprazole, and placebo groups (1.78, 1.18, 1.18, and 2.10 msec, respectively). None of the changes observed in the ECG parameters were considered to be clinically relevant.

Mean changes from baseline: Long-term, Controlled Trial 331-10-232

Table 4 Mean (SD) Change from Baseline in Electrocardiogram Results at Last Visit in the Double-blind Maintenance Phase of Trial 331-10-232 (Safety Sample)

ECG Parameter (Units)	Timepoint	Mean (SD)	
		Brexpiprazole	Placebo
Ventricular rate (bpm)	Baseline	68.95 (10.99)	72.38 (14.28)
	Change at last visit	2.57 (12.18)	2.11 (13.76)
PR interval (msec)	Baseline	158.16 (22.34)	158.36 (18.02)
	Change at last visit	-1.06 (11.05)	-1.44 (13.92)
QRS interval (msec)	Baseline	92.45 (6.33)	93.34 (10.05)
	Change at last visit	0.11 (6.15)	-0.03 (7.69)
QT interval (msec)	Baseline	389.01 (28.88)	383.07 (28.57)
	Change at last visit	-1.32 (26.16)	-4.00 (26.61)
QTcB interval (msec)	Baseline	413.89 (22.46)	416.36 (25.33)
	Change at last visit	4.94 (21.7)	2.48 (21.68)
QTcF interval (msec)	Baseline	405.11 (19.72)	404.58 (19.16)
	Change at last visit	2.69 (17.12)	0.22 (15.76)
QTcN interval (msec)	Baseline	406.96 (19.86)	407.02 (19.93)
	Change at last visit	3.05 (17.72)	0.77 (16.4)
RR interval (msec)	Baseline	892.76 (145.51)	861.29 (168.4)
	Change at last visit	-22.97 (144.31)	-33.49 (154.5)

Note: Baseline was defined as last value prior to treatment start. Last visit was defined as the last evaluable value at a scheduled visit.
Source:Module 5.3.5.3, SCS, Appendix 5, CT-LC-SZ-10.1.1.

Long-term, Open-label Trials

Similar to short-term and long-term controlled trials for the brexpiprazole group during double-blind treatment, there were no clinically meaningful changes from baseline at last visit in any ECG parameter in the long-term, open-label trials.

Creatine Phosphokinase Elevation and Rhabdomyolysis

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.

In short term controlled trials, in the all brexpiprazole treatment group, 7.7% of subjects had a PCR CPK value (≥3 x ULN), compared with 5.5% in the placebo group. A CPK value ≥ 5 × ULN was reported in 3.7% of subjects in the brexpiprazole 2 to 4 mg/day group compared with 2.8% in the placebo group. A CPK value ≥ 7 × ULN was reported in 1.7% of the brexpiprazole 2 to 4 mg/day group and 4.3% of the

brexpiprazole > 4 mg/day group compared with 1.9% of the placebo group. A CPK value ≥ 10 ×ULN was reported in 1.0% of the brexpiprazole 2 to 4 mg/day group compared with 1.1% of the placebo group. There was no correlation observed between the length of time IMP was taken and the elevation of CPK. Most elevations of CPK to over 1000 U/L were transient and limited to 1 time point.
During the Double blind Maintenance phase of trial 331-10-232, the incidence of PCR changes in CPK (≥ 3 × ULN) was lower in the brexpiprazole group (1 subject [1.1%]) compared with the placebo group (4 subjects [4.0%])
In the long-term, open-label trials, a total of 109 subjects (8.1%) had PCR CPK test results (≥ 3 × ULN); among these, 44 subjects (3.1%) had a PCR CPK value ≥ 5 × ULN, 27 subjects (1.9%) had a PCR CPK ≥ 7 × ULN, and 12 subjects (0.8%) had a PCR CPK ≥ 10 × ULN.
Rhabdomyolysis was reported as a TEAE in 3 brexpiprazole treated subjects in the short-term schizophrenia trials (2 in the brexpiprazole 2 to 4 mg/day group, 1 in the brexpiprazole < 2 mg/day group). All 3 events in were serious TEAEs and 2 led to discontinuation of IMP. This TEAE was considered to be severe in 2 subjects in the brexpiprazole 2 to 4 mg/day group and mild in 1 subject in the brexpiprazole < 2 mg/day group. A further event of rhabdomyolysis occurred in the aripiprazole group. In the aripiprazole group; the subject had a severe event that was a serious TEAE and resulted in discontinuation of IMP. Further examination of the subjects in the brexpiprazole groups with rhabdomyolysis reported during the short-term trials showed that none were symptomatic (eg, all were afebrile; HR and BP were stable, no urine blood, and no muscle complaints). At least one event of rhabdomyolysis possibly related to brexpiprazole occurred in brexpiprazole CDP and at least one further event for which a causal relationship with brexpiprazole may not be excluded occurred in the post-marketing setting. In the short term controlled trials, increased blood CPK was reported as a TEAE in 9 subjects (2.0%), 26 subjects (2.2%), 5 subjects (5.4%), and 8 subjects (1.1%) in the brexpiprazole < 2 mg/day, 2 to 4 mg/day, > 4 mg/day groups, and placebo group, respectively. There was 1 report of blood CPK increased as a serious TEAE, and 2 reports of blood CPK increased leading to discontinuation of IMP.
There were no TEAEs of rhabdomyolysis reported during the Stabilization and Double blind Maintenance phases of Trial 331 10 232. There were also no TEAEs associated with CPK elevations in the Investigations SOC in Double-blind Maintenance phase. In the Stabilization phase there were 6 (1.3%) subjects with a TEAE of blood CPK increased.
There were no reports of rhabdomyolysis or related events in the long-term schizophrenia trials. A total of 26 subjects (1.8%) were reported to have blood CPK increased. None were serious TEAEs, 1 was severe, and 2 resulted in discontinuation of IMP. All except 3 events resolved or were resolving. Of the 26 subjects, 7 subjects had a TEAE that was assessed as related. Onset of CPK elevation in these events varied from -14 to 383 days.

Seizures
In short term controlled trial, seizures related TEAEs were reported in two subjects each in the 2-4 mg brexpiprazole dose group (0.16%) and in placebo group (0.27%).
Patient (from study 14644A), had a severe grand mal convulsion (a single seizure) 4 days after the first dose of IMP. was hospitalised and was stable the next day. Electroencephalogram (EEG) showed no signs of active paroxysmal activity and neurological examination showed no focal symptoms. had no relevant medical history but had two episodes of nonserious agitation 4 days and 1 day prior to the convulsion. The patient recovered but was withdrawn from the study due to the event.
In long term controlled trial 331-10-232 one event of convulsion was reported in a subject treated with brexpiprazole 4 mg. Two events of seizures (one serious) occurred in long term, open label trials, both leading to withdrawal.

Somnolence
The TEAEs that were included in the search for somnolence (no SMQ exists) were the following: hypersomnia, sedation, and somnolence.

Short-term, Controlled Trials
A TEAE related to somnolence was reported by 54 subjects (4.5%) in the brexpiprazole 2 to 4 mg/day group compared with 28 (3.8%) subjects in the placebo group. There were no serious TEAEs related to somnolence and no subject discontinued from IMP due to a TEAE related to somnolence. With the exception of severe sedation in Subject (brexpiprazole 2 to 4 mg/day group), all TEAEs related to somnolence were mild or moderate in severity. Almost all events related to somnolence resolved. In Fixed dose trials, the incidence of somnolence events was higher in the 4 mg/day brexpiprazole group (4.6%), compared to lower doses (1.1%, 2.6%, and 3.1% in the brexpiprazole 0.25, 1, and 2 mg/day groups). The incidence in the placebo group was 2.9%.

Study 14644A
In study 14644A, somnolence related TEAEs were reported in 40/153 patients (26.1%) in patients treated with quetiapine, compared to 11/ 150 (7.3%) in brexpiprazole treated subjects and 12/ 161 (7.5%) in Placebo.

Study 331-07-203
In the brexpiprazole groups, somnolence was reported as follows: 0/42 subjects (0.25 mg/day, 0.0%); 3/89 subjects (1.0 ± 0.5 mg/day, 3.4%); 3/90 subjects (2.5 ± 0.5 mg/day, 3.3%); and 5/93 subjects (5.0 ± 1.0 mg/day, 5.4%). Somnolence was reported in 2/95 placebo subjects (2.1%) and 0/50 aripiprazole subjects (0.0%).
In the brexpiprazole groups, sedation was reported as follows: 2/42 subjects (0.25 mg/day, 4.8%); 1/89 subjects (1.0 ± 0.5 mg/day, 1.1%); 3/90 subjects (2.5 ± 0.5 mg/day, 3.3%); and 4/93 subjects (5.0 ± 1.0 mg/day, 4.3%). Sedation was reported in 0/95 placebo subjects (0%) and 2/50 aripiprazole subjects (4.0%).

Long-term, Controlled Trial 331-10-232
There were no reports of somnolence, hypersomnia, or sedation within the Nervous System Disorders SOC in any treatment group during the Double-blind Maintenance phase of the trial.

Long-term, Open-label Trials
A TEAE related to somnolence was reported by 60 subjects (4.2%) in the long-term open-label trials; 45 subjects (3.2%) had somnolence, 13 subjects (0.9%) had sedation and 2 subjects (0.1%) had hypersomnia. One subject was discontinued from IMP due to a TEAE related to somnolence. There was 1 serious TEAE related to somnolence; Subject experienced moderate somnolence that was considered to be not related to IMP, and which resulted in hospitalization. The dose of IMP was not changed and the event resolved. Of the 45 subjects, 1 subject reported somnolence/drowsiness that was assessed as severe.

Suicidality
In **short-term, controlled Trials**, TEAEs related to suicidality were reported by 8 subjects (0.5%) in the all brexpiprazole treatment group and 3 subjects (0.4%) in the placebo group. The only two serious events related to suicidality (suicidal ideation and suicide attempt) both occurred among brexpiprazole treated subjects and were considered related to IMP by the investigator; in one event (suicide attempt 5 days after the first dose of IMP, Patient from study 14644A,) the drug was withdrawn and the event

resolved. PANSS total score was 87 at the Screening Visit and increased during the study; the last available measure was a PANSS total score of 105 at Visit 3. The patient had a score of 2 on the actual suicide attempts (based on the C-SSRS assessment at the Screening Visit) and the C-SSRS scores were not improved. Seven of the 8 events occurred in fixed dose trials, with no evidence of dose dependency, even though the limited number of events do not allow to draw any firm conclusion.
Analyses of the C-SSRS indicated that 3 brexpiprazole treated subjects had treatment-emergent suicidal behavior during the short-term trials, compared to one subject in placebo.
Treatment-emergent suicidal ideation was assessed in a similar percentage of the all brexpiprazole (53 subjects, 3.0%) and placebo (26 subjects, 3.5%) groups.

Long term controlled trial 331-10-232: During the Stabilization Phase there was no treatment-emergent suicidal behavior as measured by elements in the C-SSRS. The emergence of suicidal ideation was reported in 23/464 (5.0%) subjects, and the emergence of serious suicidal ideation was reported in 3/464 (0.6%) subjects according to the C-SSRS.
The incidence of TEAEs associated with suicidality was lower in the brexpiprazole group compared with the placebo group during the Double blind Maintenance phase of Trial 331 10 232. Two subjects (1.9%) in the placebo group experienced suicidal ideation during the Double-blind Maintenance phase of the trial; there were no reports of TEAEs associated with suicidality in the brexpiprazole group.
Analysis of the C-SSRS indicated that 1 (1.0%) subject in the brexpiprazole group had treatment-emergent suicidal ideation compared with 4 (3.8%) subjects in the placebo group during the Double blind Maintenance phase of the trial. No subjects in either treatment group had treatment-emergent suicidal behavior or serious suicidal ideation based on the C-SSRS. One subject (1.0%) in the brexpiprazole group had treatment emergent worsening of suicidal ideation during the Maintenance phase.

In **long-term, Open-label Trials**, TEAEs related to suicidality were reported for 23 subjects (1.6%). Suicidal ideation was reported in 16 subjects (1.1%); self injurious behavior in 3 subjects (0.2%); suicide attempt and intentional self-injury in 2 subjects each (0.1%); and intentional overdose and completed suicide in 1 subject each (0.1%). Five subjects had a TEAE related to suicidality that was assessed as severe. Per the C-SSRS, a total of 4 subjects (0.3%) had treatment-emergent suicidal behavior. Assessing the highest level of suicidal behavior, there were 3 subjects with actual attempts and 1 subject with aborted attempt.

Ongoing Trials
In the ongoing, open-label MDD Trial 331-10-238, 8 subjects were discontinued from IMP due to somnolence.
There were two reports of TEAEs related to VTEs in the short-term, controlled trials. Subject (Trial 331-10-002, brexpiprazole 2 to 4 mg/day group) was discontinued from IMP on Day 2, and experienced deep vein thrombosis on Day 15 and pulmonary embolism on Day 17. Both events were considered to be not serious, related to IMP, and resolved. The pulmonary embolism was rated as severe in intensity. No action was taken with IMP for either event.

Venous Thromboembolytic Events
Short-term, Controlled Trials
There were two reports of TEAEs related to VTEs in the short-term, controlled trials. Subject (Trial 331-10-002, brexpiprazole 2 to 4 mg/day group) was discontinued from IMP on Day 2, and experienced deep vein thrombosis on Day 15 and pulmonary embolism on Day 17. Both events were considered to

be not serious, related to IMP, and resolved. The pulmonary embolism was rated as severe in intensity. No action was taken with IMP for either event.
There were no events of VTE reported in Long-term controlled Trial 331-10-232 and in long-term, open-label trials.

Serious adverse events and deaths

Deaths in the brexpiprazole CDP
In controlled schizophrenia clinical trials, no deaths occurred in the PBO arm, compared with three deaths (0.1%) in brexpiprazole arms (one found dead 12 days after the end of a 6 weeks brexpiprazole trial, cause of death unkown, considered unlikely related to IMP by the investigator; one: death due to 12 days after the end of a 6 weeks brexpiprazole trial, considered not related to IMP by the investigator; one: death due to in the single blind stabilization phase of the long term trial, considered not related to IMP by the investigator). Other 6 deaths occurred in schizophrenia open-label trials (gastric ulcer perforation/peritonitis , with no confounding factors, treated with brexpiprazole 2 mg, septic shock, cardiac failure, coronary artery disease, completed suicide, uterine cancer), all considered not drug related by the investigators.
In MDD trials no deaths occurred during the controlled treatment period, while 7 subjects died during the long term open label brexpiprazole trials (2 cases of completed suicide; one case each of: metastatic malignant melanoma, pulmonary embolism, gastric ulcer perforation/peritonitis, ovarian cancer, acute myocardial infarction/ myocardial rupture), all considered not drug related by the investigator, apart from one case of completed suicide considered possibly related. Six further cases of death (out of 548 randomized subjects, 1%) occurred in AD subjects whosetreatment remains blinded in ongoing trials, (one case each of: intracranial haemorrhage, aspiration pneumonia, dementia Alzheimer's type, obstructive airways disorder, encephalitis and brain oedema/ vascular encephalopathy) all considered not related by the investigators, apart from the case of intracranial haemorrhage considered unlikely related to IMP by the investigator.

Table 42: List of Subject Deaths – Schizophrenia

Trial/ Subject	Treat-ment Group/ Dose	Age/ Gender/ Race	AE PT	Day of Last IMP Dose	Day of Death	Relatedness to IMP[a]	Autopsy/ Confounding Factors[b]
Schizophrenia (Completed Short-term, Controlled Trials)							
[redacted]	Brex 5 mg/day	[redacted]	Death[c]	42	54	Unlikely related	No/ Obesity; GERD; long-term NSAID use
	Brex 4 mg/day		[redacted]	41	54	Not related	No/ [redacted]
Schizophrenia (Completed Long-term, Double-blind Trial) (Single-blind Stabilization Phase)							
[redacted]	Brex 4 mg/day	[redacted]	[redacted]	152	162	Not Related	Not available/ [redacted]
Schizophrenia (Completed Long-term, Open-label Trials)							
[redacted]	Brex 2 mg/day	[redacted]	Gastric ulcer perforation/ Peritonitis	1	2	Not related	Yes/ No confounding factors
	Brex 3 mg/day		Septic shock	293	316	Not related	No/ History of MRSA, VRE, tuberculosis, and atypical mycobacterium
[redacted]	Brex 2 mg/day	[redacted]	Cardiac failure	206	213	Not related	No/ Obesity (BMI: 30.9 kg/m^2), hypertension
	Brex 4 mg/day		Coronary artery disease	394	423	Not related	No/ Underlying schizophrenia, history of atrial fibrillation, anemia, COPD, heavy smoking, and sedentary lifestyle

[redacted]	Brex 3 mg/day	[redacted]	Septic shock	293	316	Not related	No/ History of MRSA, VRE, tuberculosis, and atypical mycobacterium
[redacted]	Brex 2 mg/day	[redacted]	Cardiac failure	206	213	Not related	No/ Obesity (BMI: 30.9 kg/m^2), hypertension
[redacted]	Brex 4 mg/day	[redacted]	Coronary artery disease	394	423	Not related	No/ Underlying schizophrenia, history of atrial fibrillation, anemia
[redacted]	**Treat-ment Group/ Dose**	[redacted]	**AE PT**	**Day of Last IMP Dose**	**Day of Death**	**Relatedness to IMP[a]**	**Autopsy/ Confounding Factors[b]**
[redacted]	Brex 3 mg/day	[redacted]	Completed suicide	173	173	Not related	No/ Underlying schizophrenia, psychosocial dysfunction
[redacted]	Brex 4 mg/day	[redacted]	Uterine cancer	33	[redacted]	Not related	Not available/ No confounding factors

Table 43 : List of Subject Deaths – MDD

Trial/ Subject	Treat-ment Group/ Dose	Age/ Gender/ Race	AE PT	Day of Last IMP Dose	Day of Death	Relatedness to IMP[a]	Autopsy/ Confounding Factors[b]
MDD Adjunctive Therapy (Long-term, Open-label Trials[f])							
[redacted]	Brex 0.75 mg/day	[redacted]	Metastatic malignant melanoma	54	135	Not related	No record/ Melanoma upper chest 2000
[redacted]	Brex 1 mg/day	[redacted]	Completed suicide	78	80	Possibly related	Yes/ Long history of MDD
[redacted]	Brex 0.5 mg/day	[redacted]	Completed suicide	231	231	Not related	No record/ Underlying MDD, loss of job, immediate social stressors
[redacted]	Brex 1 mg/day	[redacted]	Pulmonary embolism	112	119	Not related	No record/ Family and personal history of pulmonary embolism; hypertension
[redacted]	Brex 3 mg/day	[redacted]	Gastric ulcer perforation/ Peritonitis	241	241	Not related	Yes/ Long-term NSAID use; ranitidine since 2009; medical history of GERD
[redacted]	Brex 1 mg/day	[redacted]	Ovarian cancer	79	270	Not Related	No Record/ Family history of breast cancer; history of ovarian cyst
MDD Adjunctive Therapy (Long-term, Elderly Trial)							
[redacted]	Brex 2 mg/day	[redacted]	Acute myocardial infarction/Myocardial rupture	182	193	Not related	Yes/ Advanced age, medical history included tachycardia and arteriosclerosis

Other Serious Adverse Events

Table 44 Serious TEAEs by SOC and PT (Safety Sample: Short-term, Controlled Trials - Schizophrenia)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects						
	Brexpiprazole				Placebo (N = 740)	ARI (N = 50)	QUET (N = 153)
	< 2 mg (N = 456)	2 - 4 mg (N = 1199)	> 4 mg (N = 93)	ALL (N = 1748)			
Subjects With Any Serious Treatment Emergent Adverse Events	18 (3.9)	37 (3.1)	4 (4.3)	59 (3.4)	31 (4.2)	2 (4.0)	2 (1.3)
Blood and Lymphatic System Disorders							
Eosinophilia	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Disorders							
Acute Myocardial Infarction	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders							
Gastric Ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Gastric Ulcer Haemorrhage	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
General Disorders and Administration Site Conditions							
Death	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, Poisoning and Procedural Complications							
Ankle Fracture	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations							
Blood Creatine Phosphokinase Increased	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Electroencephalogram Abnormal	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and Nutrition Disorders							
Hypoglycaemia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Type 2 Diabetes Mellitus	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders							
Rhabdomyolysis	1 (0.2)	2 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)	1 (2.0)	0 (0.0)
Nervous System Disorders							
Complex Partial Seizures	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Dizziness	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Generalised Tonic-Clonic Seizure	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Psychiatric Disorders							
Acute Psychosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Aggression	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Irritability	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Psychiatric Symptom	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Psychotic Disorder	2 (0.4)	4 (0.3)	1 (1.1)	7 (0.4)	5 (0.7)	0 (0.0)	1 (0.7)
Schizophrenia	11 (2.4)	24 (2.0)	2 (2.2)	37 (2.1)	22 (3.0)	0 (0.0)	1 (0.7)
Suicidal Ideation	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Suicide Attempt	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects						
	Brexpiprazole				Placebo (N = 740)	ARI (N = 50)	QUET (N = 153)
	< 2 mg (N = 456)	2 - 4 mg (N = 1199)	> 4 mg (N = 93)	ALL (N = 1748)			
Respiratory, Thoracic and Mediastinal Disorders							
Asphyxia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders							
Angioedema	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Module 5.3.5.3, SCS, Appendix 4, CT-ST-SZ-6.6.1.

Serious Adverse Events in Phase 3 Fixed-Dose Trials 331-10-230, 331-10-231, and 331-10-002

There were 40 brexpiprazole-treated subjects in the fixed-dose trials that experienced a serious TEAE. At least one serious TEAE occurred in 4.4%, 4.7%, 2.9%, 2.3% and 4.5% in subjects treated with brexpiprazole 0.25 mg, 1mg, 2 mg, 4 mg/ day group and PBO, respectively. Most subjects (37/40 subjects in brexpiprazole groups and 20/22 subjects in placebo group) had events in the Psychiatric Disorders SOC that were related to the underlying condition (ie, acute psychosis, aggression, irritability, psychiatric symptom, psychotic disorder, schizophrenia, or suicidal ideation). Other serious TEAEs in subjects in the brexpiprazole groups consisted of 1 subject in the 0.25 mg/day group (subject) with acute myocardial infarction, which was severe, not related to IMP, and resulted in discontinuation of IMP, and 1 subject in the 2 mg/day group (Subject) with rhabdomyolysis, which was severe, unlikely related to IMP, resulted in discontinuation of IMP, and resolved.

Serious Adverse Events in Long-term, Controlled Trial 331-10-232

In the Stabilization 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 Stabilization phase. One subject had a fatal serious TEAE during the Stabilization 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.

Table 45: Serious TEAEs by SOC and PT for the Double-blind Maintenance Phase of Trial 331-10-232 (Safety Sample)

Table 2.7.4.2.1.3.3-1 Serious TEAEs by SOC and PT for the Double-blind Maintenance Phase of Trial 331-10-232 (Safety Sample)		
System Organ Class MedDRA Preferred Term	Brexpiprazole (1 - 4 mg) (N = 97) n (%)	Placebo (N = 104) n (%)
At least 1 serious TEAE	3 (3.1)	11 (10.6)
Cardiac disorders	0 (0.0)	2 (2.0)
Angina unstable	0 (0.0)	1 (1.0)
Arrhythmia	0 (0.0)	1 (1.0)
Investigations	1 (1.0)	0 (0.0)
Hepatic enzyme increased	1 (1.0)	0 (0.0)
Psychiatric disorders	2 (2.1)	10 (9.6)
Psychotic disorder	1 (1.0)	4 (3.9)
Schizophrenia	1 (1.0)	5 (4.8)
Suicidal ideation	0 (0.0)	1 (1.0)
Vascular Disorders	0 (0.0)	1 (1.0)
Hypertension	0 (0.0)	1 (1.0)

Source: Module 5.3.5.3, SCS, Appendix 5, CT-LC-SZ-6.6.1.

Serious Adverse Events in Long-term, Open-label Trials

The overall incidence of serious TEAEs in the long-term, open-label trials was 13.5%. Similar to results seen in the short-term trials, the highest incidence of serious TEAEs in the long-term trials (11.4% of subjects) occurred in the Psychiatric Disorders SOC, reflective of the underlying disease. Most other serious TEAEs in other SOCs were experienced by only 1 subject.

Twenty-three subjects had schizophrenia reported as serious TEAEs that were considered related to IMP; other serious TEAEs assessed as related to IMP were akathisia (4 serious TEAEs), psychotic disorder (3 serious TEAEs), and 1 serious TEAE each of anxiety, cardiac failure congestive, general tonic-clonic seizure, aggression, panic attack, extrapyramidal disorder, and diabetic ketoacidosis.

Serious Adverse Events in the All Brexpiprazole Trials Group

The overall incidence of serious TEAEs in the All Brexpiprazole Trials group was 5.8% (406/7020 subjects). The highest incidence of serious TEAEs occurred in the Psychiatric Disorders SOC (4.2% of subjects), with 3.0% of subjects reporting schizophrenia. Serious TEAEs were reported in 0.4% of subjects in the Nervous System Disorders SOC. The percentage of subjects who reported a serious TEAE was 9.9% for subjects with schizophrenia (313/3170) and 2.5% for subjects with MDD (93/3672); none of the subjects with ADHD (0/155) or PTSD (0/23) experienced a serious TEAE. The investigator considered the majority (> 69%) of serious TEAEs to be not related to IMP.

Serious Treatment-emergent Adverse Events in the Clinical Pharmacology Trials Group

In the All Clinical Pharmacology Trials group, there were no deaths. A serious TEAE was reported by 4 brexpiprazole subjects (0.5%) and no placebo subjects.

Table 46： List of Subjects with Serious TEAEs in Clinical Pharmacology Trials (Safety Sample: All Clinical Pharmacology Trials)

Subject (Indication)	Age/Gender/ Race	TEAE (MedDRA PT/VT)	Trial Day of Onset	Causality/Action Taken with IMP
[redacted] (Schizophrenia)	[redacted]	Drug hypersensitivity/ Allergic reaction to study medication	2	Related/ Drug withdrawn
[redacted] (Schizophrenia)		Anxiety/Anxiety attack	17	Unlikely related/ Dose not changed
[redacted] (MDD)		Extrapyramidal disorder/ Extra pyramidal side effects	8	Possibly Related/ Drug withdrawn
[redacted] (Schizophrenia)		Schizoaffective disorder/ Worsening of schizoaffective disorder	22	Not related/ Dose not changed

B = Black; F = female; M = male; VT = verbatim term; W = White.
Source: Module 5.3.5.3, SCS, Appendix 8, CT-CP-6.2.

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.

Serious Adverse Events in Ongoing Trials

Serious TEAEs reported during ongoing trials as of the data cutoff date of 31 Aug 2016 have been cited among safety topics of interest, where relevant.

Laboratory findings

Hepatic parameters

In short-term, Controlled Trials no relevant difference between brexpiprazole and placebo were observed in the percentages of subjects with PCR hepatic values.

In Long-term, Controlled Trial 331-10-232, a higher frequency of potentially clinically relevant elevations in ALT and AST of ≥ 3 × ULN [in 2 (2.2%) and 3 (3.3%)] were reported in brexpiprazole treated subjects compared to PBO subjects [1 (1.0%) and 0].

In Long-term, Open-label Trials, two (0.1%) subjects had ALT ≥10 × ULN and 3 (0.2%) subjects had ALT ≥5 × ULN. Values for AST ≥10 × ULN were reported in 1 (0.1%) subject; AST ≥ 5 × ULN was reported in 6 (0.4%) subjects. One subject met Hy's Law criteria (ALT > 3 × ULN or AST > 3 × ULN and total bilirubin > 2 × ULN).

The incidence of subjects who reported TEAEs related to hepatic function was similar in the brexpiprazole 2-4 mg and placebo group in short term controlled trials (1.8% vs 1.9%).

Five brexpiprazole treated subjects discontinued from IMP due to TEAEs related to hepatic function (0.3%) (PTs: 1 drug induced liver injury, 3 hepatic enzyme increased and one aspartate aminotransferase increased), compared to two discontinuations in the PBO group (0.3%) (PTs: 2 liver function test increased). Among the 5 brexpiprazole treated subjects, one subject had hepatic enzyme elevation prior to treatment with IMP, one subject had a confounding factor/ alternative explanation (chronic cholecystitis and cholelithiasis) and in one subject hepatic enzyme elevation temporally corresponded to CPK elevation and blood lactate dehydrogenase increased).

In the fixed-dose short term controlled trials no clear dose-dependency was observed in the incidence of TEAEs for hepatic impairment (0, 0.9%, 2.1%, 1.5% and 2.5% in the brexpiprazole 0.25 mg/day, 1

mg/day, 2 mg/day, and 4 mg/day groups, and in the placebo group), even though the limited number of events do not allow to draw any firm conclusions.
In the maintenance phase of long term controlled trial 331-10-232, hepatic enzymes increased, ALT increased, and nonalcoholic steatohepatitis were each reported for 1 (1.0%) subject in the brexpiprazole group; there were no TEAEs associated with hepatic function reported in the placebo group. The subject with non alcoholic steatohepatitis discontinued brexpiprazole treatment due to the event, which was considered unrelated to IMP. The event of hepatic enzymes increased was reported as serious but was assessed as not related to IMP and did not lead to discontinuation.
The incidence of subjects who reported ≥ 1 TEAE related to hepatic function in the long term, open-label trials was 2.4%, slightly higher than the incidence in the all brexpiprazole treatment group in the short term, controlled trials (1.4%).
A TEAE related to hepatic function was reported in 34 subjects, among whom 8 were discontinued (liver disorder, ALT increased, hypertransaminasemia, hyperbilirubinemia, ALT increased, AST increased, and blood bilirubin increased and hepatic function abnormal. The most frequently reported TEAE was ALT increased, which was reported for 10 (0.7%) subjects.
One subject in the open label trial 14644B, experienced the serious TEAEs of ALT increased, AST increased, and blood bilirubin increased on Day 151. That day, the subject met the PCR criteria for alkaline phosphatase, ALT, and AST. The events were considered by the investigator to be not related, severe in intensity, and not resolved. IMP was discontinued.

Ongoing Trials

Discontinuation of IMP due to a TEAE of ALT increased was reported for 3 subjects in the ongoing, open-label MDD Trial 331-10-238.
Discontinuation of IMP due to TEAEs of AST increased and GGT increased were reported for at least 1 subject each in ongoing, long-term, open-label MDD Trial 331-10-238. Discontinuation of IMP due to the nonserious TEAE of hepatic enzyme increased was reported for 1 subject in the ongoing agitation in AD Trial 331-12-284.

Changes in Creatine Phosphokinase, Glucose, Lipids, Prolactin, White blood cells

See dedicated sections among safety topics of special interest

Other laboratory findings

Mean changes from baseline to last visit, incidence of PCR values, and associated TEAEs reported for all hepatic and renal parameters, electrolytes, hematology and coagulation factors, urinalysis parameters, and adrenocorticotropic hormone, cortisol and thyroid stimulating hormone were similar among treatment groups in all trials and not clinically meaningful.

Vital Signs Parameters

Mean changes from baseline to last visit for vital signs (heart rate, systolic blood pressure, and diastolic blood pressure) were small, similar in brexpiprazole treatment group compared with placebo group in controlled trials and not considered clinically meaningful.
Orthostatic hypotension, dizziness, and syncope are discussed as safety topics of interest.
The percentages of subjects with PCR changes in other vital signs were similar in brexpiprazole treatment group compared with placebo group in controlled trials.

Electrocardiograms

See section dedicated to QT prolongation

Safety in special populations

Elderly

After single-dose administration of brexpiprazole to elderly (≥ 65 years) and adult (18 to 45 years) subjects in a clinical pharmacology trial, brexpiprazole exposure (maximum plasma concentration [Cmax] and area under the concentration-time curve from time zero to infinity [AUC∞]) was similar in both age groups. Based on the results of the population pharmacokinetics (PK) analysis, age was identified as a statistically significant covariate on apparent central volume of distribution (Vc/F); the effect of age on Vc/F within the 5th and 95th percentiles of the population was -19% to 14%, and not considered clinically relevant.

Table 5: Summary of Demographic Characteristics (Randomized Sample: Short-term, Controlled Trials - Schizophrenia)

Demographic Characteristic	Brexpiprazole				Placebo (N = 742)	ARI (N = 50)	QUET (N = 154)
	< 2 mg (N = 456)	2 - 4 mg (N = 1201)	> 4 mg (N = 93)	ALL (N = 1750)			
Age (yrs)							
n	456	1201	93	1750	742	50	154
Mean (SD)	40.9 (11.3)	39.9 (11.2)	39.5 (11.1)	40.1 (11.2)	40.5 (11.2)	40.8 (11.0)	41.1 (10.9)
Range	18, 65	18, 65	19, 58	18, 65	18, 64	19, 61	20, 65
Age Range [n (%)]							
< 50	341 (74.8)	938 (78.1)	71 (76.3)	1350 (77.1)	561 (75.6)	39 (78.0)	111 (72.1)
50 - 64	113 (24.8)	260 (21.6)	22 (23.7)	395 (22.6)	181 (24.4)	11 (22.0)	42 (27.3)
≥ 65	2 (0.4)	3 (0.2)	0 (0.0)	5 (0.3)	0 (0.0)	0 (0.0)	1 (0.6)

The use of brexpiprazole in elderly patients with schizophrenia was not systematically investigated in a dedicated trial.

A dedicated 26-week, open label trial (Trial 16160A) enrolled 132 elderly patients (mean age of the patients was 71 years; 26% were ≥75 years), with the primary objective to evaluate the long-term safety and tolerability of brexpiprazole (1 to 3 mg/day) as adjunct treatment to anti depressive treatment in elderly patients with MDD. The mean modal and mean doses of brexpiprazole were 1.91 mg/day and 1.80 mg/day, respectively.

Approximately 77% of the patients had one or more TEAEs. The TEAEs with the highest incidences were fatigue (15%), restlessness (13%) and increased appetite (10%) followed by akathisia, weight increased, anxiety and dizziness (all approximately 8%). The overall incidence of patients with severe TEAEs was 8%. A total of 6 patients (4.5%) had 11 SAEs; 2 patients had in total 5 SAEs that were considered related to brexpiprazole by the investigator: One patient had hypotension and worsening of depression and the other patient had fall, facial bones fracture, and eye contusion. A total of 25 patients (19%) were withdrawn from the study due to TEAEs. The most common TEAE leading to withdrawal was fatigue (3.0% of patients). The proportion of patients with EPS-related TEAEs was 16% (21 patients); the 21 patients had 30 events; most patients had akathisia (11 patients) and tremor (9 patients). An increase in mean prolactin level was seen during the study, predominantly in women; 16% of patients had PCS high plasma level for prolactin. There were no consistent clinically relevant findings seen with other laboratory parameters during the study (including fasting glucose and lipid values), vital signs, weight, or ECG parameter values. A mean increase in weight (0.9kg) was noted from baseline to Week 26 for those with a Week 26 assessment; a mean increase of 0.8kg from baseline to last assessment was noted. Among patients with post baseline assessment of metabolic syndrome, a total of 18 out of

89 patients fulfilled criteria for metabolic syndrome at last visit; however, 8 of them fulfilled the criteria already at baseline. 5 patients met criteria at baseline, but not at the last visit, and 66 patients had unchanged status, all suggesting no consistent shift following long-term exposure to brexpiprazole. Only a minimal change on the MMSE was seen; the mean score changed from 28.7 to 28.5 during the study.

Pregnancy
Neonates whose mothers are exposed to antipsychotic drugs, like brexpiprazole, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms.
No adequate or well controlled trials with brexpiprazole have been conducted in pregnant women. No confirmed pregnancies were reported during the short-term schizophrenia trials. Six pregnancies were reported in the long-term trials: 2 in the controlled trial and 4 in the open-label trials. Five of the 6 subjects were exposed to brexpiprazole. As of the data cutoff date (31 Aug 2016), follow-up information was available for 3 of the 6 pregnancies. There was one spontaneous abortion (subject randomized to placebo), 1 elective abortion, and 2 live births of normal infants with no complications reported during either delivery. Of the 2 remaining pregnancies, one subject was lost to follow-up and no further information was as yet available for the other subject.

Adverse Events by Metabolizer Status
In fixed-dose schizophrenia trials there were only 16 subjects CYP2D6 poor metabolizers.
A comparison of the TEAEs from the 3 phase 3, fixed-dose schizophrenia trials showed that the incidence of subjects who received brexpiprazole 2 to 4 mg/day who reported ≥ 1 TEAE was 62.5% in CYP2D6 PM (10 of 16) and 60.5% in CYP2D6 EM (150 of 248). When evaluating individual TEAEs, there were no events that seemed to be predominantly or exclusively reported in PM subjects. The interpretation of this finding should be made with consideration for the small number of PM subjects overall (n = 16).
Although no clinically meaningful differences were observed with respect to the intrinsic factor of CYP2D6 metabolizer status (poor versus extensive), a dose adjustment to one-half the maintenance dose is recommended in subjects with known CYP2D6 PM status to account for higher expected concentrations (up to 2-fold) in these subjects.

Adverse Events for Subjects with Hepatic Impairment
Short term controlled Phase 2-3 studies excluded patients with hepatic impairment (exclusion criteria: AST or ALT ≥2 x ULN), thus brexpiprazole safety in schizophrenic subjects with hepatic impairment has not been evaluated
The only information on subjects with hepatic impairment come from the few subjects enrolled in the Phase 1 Trial 331-09-225, receiving a single 2 mg oral dose of brexpiprazole (see PK section).
In Trial 331-09-225, subjects (n=22) with hepatic impairment (Child-Pugh classification as mild, moderate, and severe) were administered an open-label dose of 2 mg brexpiprazole and followed for 8 days with the objective of evaluating PK. The incidence of subjects reporting ≥ 1 TEAE was 31.8% in subjects with hepatic impairment and 26.1% in subjects with normal hepatic function. For patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

Adverse Events for Subjects with Renal Impairment
Short term controlled Phase 2-3 studies excluded patients with renal impairment (exclusion criteria: creatinine ≥2 mg/dL in all studies, apart from study 14644A: serum creatinine value >1.5 upper limit of

the reference range), thus brexpiprazole safety in schizophrenic subjects with renal impairment has not been evaluated.
The only information on subjects with Renal Impairment come from the few subjects enrolled in the Phase 1 Trial 331-09-226 receiving a single dose of 3 mg brexpiprazole. In Trial 331-09-226, subjects (n=10) with severe renal impairment were administered an open-label dose of 3 mg brexpiprazole and followed for 8 days with the objective of evaluating PK. Pharmacokinetic results showed modest increases (68%) in brexpiprazole exposure while no effect on brexpiprazole Cmax was observed in subjects with severe renal impairment. Somnolence was reported in 3/10 subjects (30%) with renal impairment and orthostatic hypotension was reported by 2/10 subjects (20%) with renal impairment (one event severe), while no such event occurred in normal subjects (n=9). Subject in the renally impaired group had a TEAE of orthostatic hypotension on Day 1 at 5 hours postdose that was assessed as severe and related to IMP.
For patients with moderate, severe or end-stage renal impairment (creatinine clearance CLcr < 60 mL/minute), the maximum recommended dosage is 3 mg once daily for patients with schizophrenia.

Adverse Events by Gender

Short-term, Controlled Trials

In short term controlled trials, among brexpiprazole treated patients 59% (1041/1748) of subjects were males. Among placebo treated subjects 57% (429/740) were males.
In the brexpiprazole 2 to 4 mg/day group, the incidence of subjects who reported ≥ 1 TEAE was 61.9% for male subjects and 58.9% for female subjects.
The incidence between genders was similar for the most frequently reported TEAEs (TEAEs reported by ≥ 5% of subjects), apart from vomiting which occurred among female brexpiprazole treated subjects in 5.3%, 4.6% and 6.4% compared to 0, 1.4% and 1.1% in males in >4mg, 2-4 mg and <2 mg groups respectively; no difference between genders was observed in the frequency of vomiting among placebo treated subjects (2.6% vs 3.0%).
Nausea occurred more frequently among female brexpiprazole treated subjects in 4.8%, 4.8% and 10.5% compared to 1.1%, 2.8% and 3.6% in males in <2mg, 2-4 mg and >4 mg groups respectively; no difference between genders was observed in the frequency of nausea among placebo treated subjects (2.2% vs 3.1%).
Similarly headache occurred more frequently among female brexpiprazole treated subjects in 12.3%, 10% and 10.5% compared to 6.3%, 8.8% and 5.5% in males in <2mg, 2-4 mg and >4 mg groups respectively; the frequency of headache among placebo treated subjects was 10.5% in males vs 7.4% in females.
Based on the results of the population PK analysis, female subjects were predicted to have 22% smaller apparent Vc/F and 20% lower apparent clearance compared with male subjects, leading to 25% higher brexpiprazole area under the concentration-time curve during the dosing interval at steady state (AUC_{τ}).

Long-term, Controlled Trial 331-10-232

In the brexpiprazole group, the incidence of subjects who reported ≥ 1 TEAE was 48.3% for male subjects and 35.9% for female subjects. The incidence between genders was higher in males for headaches (8.6% vs 2.6%) and insomnia (8.6% vs 0); whereas it was similar for the other most frequently reported TEAEs (TEAEs reported by ≥ 5% of subjects). The higher frequency in males for headache was observed also in PBO treated subjects (14.1% vs 2.5%), while insomnia among PBO treated patients occurred more frequently in females (males 3.1% vs females 15%).

Long-term, Open-label Trials
The incidence of subjects who reported ≥ 1 TEAE was 38.4% for male subjects (n = 799) and 41.8% for female subjects (n = 627). For the TEAEs reported by ≥ 5% of subjects, the incidence of insomnia was 9.1% in male subjects compared with 7.2% in female subjects. Nasopharyngitis and headache were reported at a higher incidence in female subjects (8.9% and 8.5%, respectively) compared with male subjects (4.5% and 6.3%, respectively). There was no clinically meaningful difference in incidence between the genders for other TEAEs.

Adverse Events by Race Group
Short-term, Controlled Trials
In the brexpiprazole 2 to 4 mg/day group, the incidence of subjects who reported ≥ 1 TEAE was 51.9% in white subjects and 70.5% in subjects in all other races. The frequently reported TEAEs of akathisia, diarrhea, headache, and weight increased all occurred more often in other races than in white subjects. Agitation and insomnia were more frequent in white subjects than in subjects of other races. There was no clinically meaningful difference in incidence between the race groups for other TEAEs.
Of note, the population PK analysis did not identify race as a covariate in brexpiprazole PK parameters.

Long-term, Controlled Trial 331-10-232
In the brexpiprazole group, the incidence of subjects who reported ≥ 1 TEAE was 38.7% in white subjects and 51.4% in subjects in all other races. The commonly reported TEAEs of headache occurred more often in white subjects than in other races. There was no clinically meaningful difference in incidence between the race groups for other TEAEs.

Long-term, Open-label Trials
The incidence of subjects who reported ≥ 1 TEAE was 35.2% in white subjects (n = 754) and 45.2% in subjects in all other races (n = 304). For the TEAEs reported by ≥ 5% of subjects, headache was more frequently reported in white subjects (8.6%) compared with subjects in all other races (5.7%). Nasopharyngitis, akathisia, insomnia, and schizophrenia were reported more frequently in subjects of other races (10.9%, 7.9%, 10.4%, and 16.1%, respectively) compared with white subjects (2.5%, 3.7%, 6.4%, and 12.6%, respectively). There was no clinically meaningful difference in incidence between the race groups for the TEAE of headache.

Extrinsic Factors

Adverse Events by Geographic Region
Short-term, Controlled Trials
In the brexpiprazole 2 to 4 mg/day group, the incidence of subjects who reported ≥ 1 TEAE was higher in North America (73.4%) and Asia (71.2%) compared to Latin America (63.5%) and Europe (46.0%). For the most frequently reported TEAEs, headache, weight increased, and akathisia were reported more frequently in North America (18.4%, 10.2%, and 9.6%, respectively) when compared with other regions.

Long-term, Controlled Trial 331-10-232
In the brexpiprazole group, the incidence of subjects who reported ≥ 1 TEAE was higher in North America (61.8%), compared with Latin America (50.0%), Asia (40.0%) and Europe (29.8%). For the most frequently reported TEAEs, headache was reported more frequently in Europe (10.6%) when compared with other regions.

Long-term, Open-label Trials

For the TEAEs reported by ≥ 5% of subjects by region, Latin America reported a higher incidence of weight increased (when compared to Asia, Europe, and North America (13.3%, 6.3%, 9.6%, 7.7%, respectively). Subjects in North America reported a lower incidence of schizophrenia when compared to Asia, Europe, and Latin America (8.9%, 20.7%, 13.8%, and 18.9%, respectively. Subjects in Europe reported a lower incidence of akathisia when compared to Asia, North America, and Latin America (3.0%, 7.5%, 7.2%, and 8.9%, respectively. Subjects in Asia reported a higher incidence of nasopharyngitis when compared to Europe, North America, and Latin America (19.8%, 2.3%, 2.8%, and 1.1%, respectively). There was no clinically meaningful difference in incidence among regions for other TEAEs.

Overdose

In Trial 331-10-242 (QT study), 56 subjects (age range 21-55 years) in the brexpiprazole 12 mg treatment arm were exposed to this dose for up to 11 days. Seven subjects out of 67 (10.4%) assigned to the 12 mg dose group discontinued due to the following TEAEs dizziness 2 subjects (3%), extrapyramidal symptoms (3 subjects), joint stiffness, akathisia, psychotic disorder, 1 subject each. There was 1 subject () in the brexpiprazole 2 to 4 mg/day group with a TEAE possibly associated with overdose. The event was an overdose of Nitrazepam, and occured on Day 43 after the trial was complete. A TEAE of intentional self-injury (VT: self mutilation [neck abrasions]) was reported for this same subject. The events were mild in severity, not related to IMP, and not serious. No action was taken with IMP. The events resolved and the subject recovered. Subject, in the same treatment group, experienced a serious TEAE of suicide attempt. The event was moderate in severity, and considered by the investigator to be related to IMP. The subject discontinued from the study, and recovered from the event. Intentional self-injury was reported for a patient (right forearm bite self inflicted) in the brexpiprazole < 2 mg /day group in the fixed dose Trial 331-10-230. The TEAE was assessed as moderate in severity, not related to IMP, and not serious. The dose of IMP was not changed. The event resolved and the subject recovered. One other subject in the < 2 mg/day group () experienced a TEAE of self injurious behavior. The event was mild in intensity, not related to IMP, and not serious. No action was taken with IMP. The event resolved and the subject recovered.

There were no reported overdoses (> 12 mg/day) of brexpiprazole in the Double-blind Maintenance phase of Trial 331-10-232, and overdoses were reported (> 12 mg/day) for 2 subjects in the long-tem, open-label Trial 331-10-237.

In long-term, open-label schizophrenia trials, TEAEs of accidental overdose were reported for 6 (0.42%) subjects. In all 6 subjects the TEAE was rated as mild in severity and the subjects recovered. The dose was not changed and all subjects continued the trial. Intentional overdose was reported for 1 subject. The intentional overdose TEAE was rated as severe and the subject recovered.

Self injurious behavior was reported for 3 subjects. The TEAE was assessed as mild or moderate in severity, all subjects recovered. The dose was not changed for 2 subjects, and was withdrawn in the third subject.

Suicide attempt was reported for 2 subjects. The TEAE was assessed as moderate in severity in 1 subject and as severe in the other subject. Both subjects recovered and were withdrawn from the trial.

Eight events of overdose with brexpiprazole have been reported to date from the postmarketing setting; none of these events was serious or resulted in any adverse outcomes.

Withdrawal and Rebound

No formal assessments of withdrawal have been conducted in human subjects.

In the short-term, controlled trials, the incidence of subjects who reported ≥ 1 TEAE in the 30-day follow-up period was 18.0% in the brexpiprazole 2 to 4 mg/day group (121 of 671 subjects), and

18.7% in the placebo group (83 of 445 subjects). The most frequently reported TEAEs were schizophrenia (16 [2.4%] subjects in the 2-4 mg brexpiprazole treatment group and 10 [2.2%] subjects in the placebo group), constipation (12 [1.8%] subjects in the 2-4 mg brexpiprazole treatment group and 4 [0.9%] subjects in the placebo group), nasopharyngitis (9 [1.3%] subjects in the all brexpiprazole treatment group and 6 [1.3%] subjects in the placebo group), and headache (9 [1.3%] subjects in the all brexpiprazole treatment group and 4 [0.9%] subjects in the placebo group).
In the long-term, controlled Trial 331-10-232, no subject in the brexpiprazole group experienced a TEAE in the 30-day follow-up period. In the placebo group the incidence of subjects who reported ≥ 1 TEAE in the 30-day follow-up period was 1.9% (2 of 104 subjects).
In the long-term, open-label trials, the incidence of subjects who reported ≥ 1 TEAE in the 30-day follow-up period was 4.9% (53 of 1074 subjects). The most frequently reported TEAE was schizophrenia (13 [1.2%] subjects) followed by back pain (3 [0.3%] subjects) and agitation (2 [0.2%] subjects); no other TEAE was reported in more than 1 subject. There was no indication of a withdrawal syndrome attributable to brexpiprazole.

Safety related to drug-drug interactions and other interactions

For effects of Other Drugs on Brexpiprazole and Effects of Brexpiprazole on the Pharmacokinetic Parameters of Other Drugs *in vitro* and in healthy subjects see PK sections.
No trials have been conducted to evaluate the concomitant administration of alcohol and brexpiprazole.

Discontinuation due to adverse events

Discontinuations in Short-term, Controlled Trials

The percentage of subjects reporting TEAEs leading to discontinuation of IMP was 8.8% (106 subjects) in the brexpiprazole 2 to 4 mg/day group and 13.1% (97 subjects) in the placebo group.
AEs leading to discontinuation of IMP were predominately in the Psychiatric Disorders SOC [9.4% (43 subjects) in the brexpiprazole <2 mg/ day group, 6.7% (80 subjects) in the brexpiprazole 2 to 4 mg/day group, 7.5% (7 subjects) in the >4 mg group and 10.5% (78 subjects) in the placebo group] and were likely related to the underlying condition (schizophrenia: 7,0%, 5.3%, 3.2% and 8.8%; psychotic disorder: 1.1%, 0.7%, 2.2% and 1.1%; agitation: 0.2%, 0.2%, 1.1% and 0.3%, hallucination: 0.2%, 0.1%, 0 and 0 in the Brexpiprazole <2 mg, 2-4 mg, >4 mg and PBO respectively).
Among subjects treated with aripiprazole 0/50 experienced AEs leading to discontinuation of IMP in the Psychiatric Disorders SOC; among subjects treated with quetiapine 4/153 (2.6%) experienced AEs leading to discontinuation of IMP in the Psychiatric Disorders SOC.
Five brexpiprazole treated subjects discontinued from IMP due to TEAEs related to hepatic function (0.3%) (PTs: 1 drug induced liver injury in a subject treated with brexpiprazole 2 mg, 3 hepatic enzyme increased -2 in subjects treated with brexpiprazole 4 mg and one in a subject treated with 2 mg/day-and one aspartate aminotransferase increased, in a subject treated with brexpiprazole 1 mg), compared to two discontinuations in the PBO group (0.3%) (PTs: 2 liver function test increased).
Other TEAEs that led to discontinuation in > 1 subject in the brexpiprazole 2 to 4 mg/day group were dizziness, rhabdomyolysis (both reported by 2 subjects each, 0.2% vs 0 events in PBO) and psychomotor hyperactivity (4 subjects in the 2-4 mg/ day group, 0.3% compared to one subject, 0.1% in PBO. A further subject treated with brexpiprazole 4 mg, discontinued due to blood creatinine phosphokinase increased and one subject in the 2 mg group discontinued due to blood triglycerides increased.
One event each of electrocardiogram QRS prolonged (2-4 mg group, 0.1%) and electrocardiogram QT prolonged (>4 mg group, 1%) leading to discontinuation occurred in brexpiprazole treated subjects, compared to one event of electrocardiogram QT prolonged in PBO (0.1%).

Among subjects treated with aripiprazole 3/50 subjects (6%) experienced TEAEs leading to discontinuation (one event each of rhabdomyolysis, alanine aminotransferase increased and complex partial seizure).
Among subjects treated with quetiapine 4/153 subjects (2.6%) experienced TEAEs leading to discontinuation (3 events of schizophrenia and one event of anxiety).

Discontinuations in Phase 3 Fixed-Dose Trials 331-10-230, 331-10-231, and 331-10-002
The incidence of TEAEs leading to discontinuation of IMP in the fixed-dose trials was 13.3% (12/90 subjects) in the brexpiprazole 0.25 mg/day group, 12.8% (30/235 subjects) in the brexpiprazole 1 mg/day group, 7.9% (38/482 subjects) in the brexpiprazole 2 mg/day group, and 10.1% (48/477 subjects) in the brexpiprazole 4 mg/day group, compared with 15.5% (75/484 subjects) in the placebo group.
AEs leading to discontinuation of IMP were predominately in the Psychiatric Disorders SOC [11.1% (10/90 subjects) in the brexpiprazole 0.25 mg/day group, 11.9% (28/235 subjects) in the brexpiprazole 1 mg/day group, 6.4% (31/482 subjects) in the brexpiprazole 2 mg/day group, and 8.0% (38/477 subjects) in the brexpiprazole 4 mg/day group, compared with 12.2% (59/484 subjects) in the placebo group] and were likely related to the underlying condition (pooled PTs schizophrenia, psychotic disorder, agitation, hallucination: 10.6%, 6.2%, 7.5% and 11.5% in the brexpiprazole 1 mg/day group, 2 mg/day group, 4 mg/day group and placebo group, respectively).
Except for these psychiatric disorders TEAEs, only hepatic enzyme increase (2 subjects [4 mg]) and psychomotor hyperactivity (3 subjects [4 mg]) were experienced by more than 1 subject in any of the brexpiprazole dose groups.
Discontinuations in Long-term, Controlled Trial 331-10-232
In the single blind Stabilization phase of the long term trial 331-10-232, the most frequently occurring TEAEs resulting in discontinuation of brexpiprazole therapy were related to the subject's underlying disease (schizophrenia). In the Double-blind Maintenance phase of Trial 331-10-232, discontinuations of IMP due to TEAEs occurred more frequently in the PBO group (11.5%) compared with the brexpiprazole group (5.2%), due to a lower incidence of discontinuations due to Psychiatric Disorders (schizophrenia, psychotic disorder, and suicidal ideation) for subjects in the brexpiprazole group.

Discontinuations in Long-term, Open-label Trials Group - Schizophrenia
In the Long-term, Open-label Trials, 226 subjects (15.9%) had a TEAE leading to discontinuation. Most subjects who discontinued IMP because of a TEAE had events in the Psychiatric Disorders SOC (182 subjects, 12.8%), such as schizophrenia (144 subjects, 10.1%), psychotic disorder (18 subjects, 1.3%), insomnia (4 subjects, 0.3%), 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 (7 subjects, 0.5%), alanine aminotransferase increased (3 subjects, 0.2%), and pregnancy (3 subjects, 0.2%).

Post marketing experience
Brexpiprazole was approved for marketing by the United States Food and Drug Administration (US FDA) in Jul 2015.
Based on an approximated 26130894 tablets of brexpiprazole distributed through 30 Sep 2016, the cumulative number of patient-years treated with marketed brexpiprazole was 71591. This estimate of patient exposure is based on the availability of monthly product distribution figures, and patient exposure estimates are based on calculations from these figures. Due to the limitations of this approach, it is not possible to reliably estimate the number of subjects treated with marketed brexpiprazole.

The postmarketing safety information for brexpiprazole was reviewed from 5 quarterly Periodic Adverse Drug Experience Reports (PADERs), covering the period from 10 Jul 2015 through 09 Oct 2016. Cumulatively through 30 Sep 2016, the most frequently reported ADRs for marketed brexpiprazole included weight increased (n = 235, of which 7 were serious), akathisia (n = 162, of which 8 were serious), and anxiety (n = 81, of which 5 were serious).
Eight (8) events of overdose with brexpiprazole have been reported to date from the postmarketing setting; none of these events was serious or resulted in any adverse outcomes. Thus, the information regarding the risk associated with an overdose of brexpiprazole remains limited.
In total, 5 cases of NMS, 4 cases of suicide attempt, 35 cases of suicidal ideation, and 4 cases of completed suicide have been reported in the postmarketing setting, with very limited data provided. A causal relationship could not be established in these cases due to lack of information regarding either indication, dose administered, treatment duration, clinical feature or course of the events.

2.1.1. Discussion on clinical safety

The brexpiprazole clinical development program (CDP) consists of trials for monotherapy of schizophrenia and as adjunctive treatment of major depressive disorder (MDD). Additionally, the CDP contains trials for brexpiprazole for monotherapy of agitation associated with Alzheimer's disease (AD) (still blinded) and adjunctive treatment of attention deficit hyperactivity disorder (ADHD) and post-traumatic stress disorder (PTSD).
As of the data cut-off date, 3450 subjects with schizophrenia have been exposed to brexpiprazole. In the entire brexpiprazole CDP, 7020 subjects in phase 2/3 trials (for MDD, schizophrenia, ADHD, and PTSD) and 877 subjects in clinical pharmacology trials have been exposed to at least 1 dose of brexpiprazole in clinical trials conducted in North America, Latin America, Europe, and Asia.
The clinical pharmacology trials conducted in the brexpiprazole CDP include diverse populations (male and female subjects, healthy subjects, subjects with psychiatric diseases [including schizophrenia, MDD, and ADHD], subjects with hepatic or renal impairment, and limited numbers of elderly subjects), different trial designs, and doses ranging from 0.2 mg/day to 12 mg/day (1 mg/day to 12 mg/day for schizophrenia).
An adequate number of patients are available to assess the short-term safety of brexpiprazole in subjects with schizophrenia compared with placebo: 1748 patients were exposed to brexpiprazole in fixed dose (Phase 3 trials: 331-10-231, 331-10-230, 331-10-002) or flexible dose (Phase 3 trial 14644A; Phase 2 Trial: 331-07-203) 6-weeks trials, compared to 740 patients randomized to placebo. Of these short-term 6 weeks brexpiprazole-treated patients, 1199 were treated with the recommended maintenance dose range requested for marketing authorization (2 mg per day to 4 mg per day). In the short term controlled trials only about half of the patients (56%, n=986) were exposed for 6 weeks (expected duration of the study). Among the most frequent reasons of discontinuation, there were AEs (9.4%), consent withdrawal (12.3%) and lack of efficacy (7.4%). Only two of these 6 weeks short-term trials included an active controlled arm: Study 14644A, a Phase 3 flexible dose study, included 153 patients treated with quetiapine XR 400-800 mg and Study 331-07-203, a fixed-flexible dose, phase 2 study included 50 patients treated with aripiprazole 15±5 mg.
The three Phase 3 fixed dose short term controlled trials –that include approximately 70% (n=1284) of subjects of the Short Term Controlled Safety Sample- evaluated the following brexpiprazole doses: 0.25 mg/day (n=90), 1 mg/day (n=235), 2 mg/day (n=482), and 4 mg/day (n=477). These pooled data by fixed dose are the only data that allow an evaluation of a dose-dependent brexpiprazole safety within the proposed therapeutic brexpiprazole dose, as in the overall Short Term Controlled Safety Sample, three integrated dose groups are presented: < 2 mg/day, 2 to 4 mg/day, and > 4 mg/day.
The only controlled long term safety data come from the 97 brexpiprazole-treated patients within the

Double-blind Maintenance phase of Trial 331-10-232 comparing brexpiprazole with placebo (n=105), administered for up to 52 weeks in subjects who were previously stabilized on brexpiprazole 1 to 4 mg/day. Thus in the interpretation of the safety data of this long-term controlled pool it must be taken in consideration that this is a selected patient population (only patients who tolerated brexpiprazole and presented the stability criteria of psychotic symptoms on brexpiprazole 1-4 mg for a consecutive period of 12 weeks were randomized in the maintenance period). Approximately half of the subjects in the brexpiprazole group (52%, n=50) completed 24 weeks of therapy during the Double-blind Maintenance phase compared with 38% of subjects (n=40) in the placebo group. Few subjects (16 brexpiprazole-treated subjects and 9 subjects in placebo group) were treated through Week 52 of the Double-blind Maintenance phase, due primarily to the early termination of the trial. Most patients (63.9%, n=62) received brexpiprazole 4 mg/ day, while 25 patients (25.8%) received brexpiprazole 3 mg/ day.

Most long-term safety data come from Open-label Trials in Schizophrenia, where 1426 patients received brexpiprazole (all doses). 846 subjects (59.3%) were exposed to ≥ 26 weeks of treatment and 654 subjects (45.8%) were exposed to ≥ 52 weeks of treatment. The most frequent modal dose was 4 mg/ day (46%, n = 663), followed by 2 mg/ day (31%, n = 442) and 3 mg/ day (20%, n = 279).

Other safety data come from the US post marketing setting, as brexpiprazole has been approved for marketing by the US FDA in July 2015, for the following two indications: adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and treatment of schizophrenia.

The schizophrenia patient population included in the safety database is not entirely representative of individuals affected by schizophrenia who are the targets of the claimed indication, as elderly subjects, subjects with psychiatric comorbidities, chronic medical illnesses -including cardiovascular diseases and Insulin-Dependent Diabetes Mellitus- subjects with substance abuse, hepatic impairment and renal impairment have been excluded from clinical trials. Furthermore, common concomitant medications used in schizophrenia were prohibited in the brexpiprazole schizophrenia protocols, thus data regarding brexpiprazole use with concomitant medication in the schizophrenia program is limited.

In the short term controlled pool similar frequencies of any TEAEs (60.7 vs 62%), occurred in brexpiprazole 2-4 mg/day group and PBO treated subjects, even though TEAEs potentially related to IMP occurred with higher frequency in brexpiprazole 2-4 mg/day group compared to PBO (55.9% vs 33%). In fixed-dose trials a dose relationship was observed for TEAE assessed as potentially related to IMP (26.8%, 29.9%, 35.6%, of subjects in the brexpiprazole 1, 2, and 4 mg/day groups respectively, compared to 30.8% in placebo groups). Severe TEAEs (5.4% vs 6.6%) and serious TEAEs (3.1% vs 4.2%) occurred with similar frequencies respectively in brexpiprazole 2-4 mg group and PBO treated subjects, with no dose-relationship observed in fixed dose trials. TEAEs leading to discontinuation of IMP occurred frequently in both treatment groups in the short term controlled pool (brexpiprazole 2-4 mg: 8.8% vs placebo: 13.5%). In both treatment groups TEAEs leading to discontinuation were predominantly in the psychiatric disorder SOC, likely related to the underlying condition (PTs schizophrenia, psychotic disorders, agitation and hallucination). In Phase 3 short term fixed dose trials TEAEs leading to discontinuation occurred with higher frequency in the brexpiprazole 4 mg/ day group (10.1%) compared to brexpiprazole 2 mg/ day group (7.9%); however TEAEs leading to discontinuation likely related to the underlying condition (PTs schizophrenia, psychotic disorders, agitation and hallucination) occurred with a lower frequency in the brexpiprazole 2 mg/day group (6.2%) and 4 mg/day group (7.5%) compared to 1 mg/ day group (10.6%) and PBO (11.5%).

In the long term maintenance phase of study 331-10-232, a higher frequency of any TEAE, TEAEs potentially related to IMP, serious TEAEs and TEAEs leading to discontinuation occurred in PBO arm compared to brexpiprazole 1-4 mg/ group. The apparently worse safety profile of the PBO arm is mainly due to lack of efficacy as a consequence of the study design; the incidence of TEAEs in the Psychiatric Disorders SOC was of 9.3% in the brexpiprazole group compared with 24.0% in the placebo group (with

the most evident differences for the PTs schizophrenia and psychotic disorders).
A higher frequency of serious TEAEs (13.5%) and TEAEs leading to discontinuation of IMP (15.8%) occurred in long term open label trials, compared to short term controlled trials. This may at least in part be a consequence of the longer exposure in long term trials, even though exposure adjusted rates of TEAEs have not been provided by the Applicant.
The most common TEAEs in the short term controlled trials, occurring ≥0.5% more often in brexpiprazole 2-4 mg treated subjects compared with PBO, where in the SOCs Nervous System Disorders (akathisia 5.6%, tremor 2.7%, dizziness 2.3% and sedation 1.9%), Gastrointestinal disorders (nausea 3.6%, diarrhoea 3.3%, abdominal pain upper 1.3%) and Investigations (weight increased 3.9%, blood CPK increased 2.2%). Most of the common TEAEs by PT occurred in fixed dose trials with higher frequency in the 4 mg dose group, compared with lower doses: akathisia (3.0%, 4.6%, 6.5% in the brexpiprazole 1 mg, 2 mg, 4 mg groups), weight increased (1.7%, 2.9%, 3.4%), diarrhea (2.1%, 3.1%, 3.8%), back pain (1.7%, 2.1%, 2.9%), dizziness (0.9%, 1.5%, 2.9%) in the brexpiprazole 1 mg, 2 mg and 4 mg groups, respectively. The types of most frequently reported TEAEs in the long term trials were similar to the short-term trials. Akathisia occurred with a higher frequency during the stabilization phase of study 331-10-232 compared to the short term controlled trials (9.1% vs 5.6%). Blood pressure has been identified as an ADR (in short term controlled trials, TEAEs of blood pressure increased occurred in 0.7% of patients in brexpiprazole 2-4 mg/ day group compared to 0.1% in PBO).
Weight increase is a common side effect of atypical antipsychotics. Weight gain is a known risk factor for the development of insulin resistance, metabolic syndrome and diabetes. Data from clinical studies clearly indicate that brexpiprazole treatment is associated with weight gain: a weight increase that met the PCR criterion (increase of ≥7% from baseline in body weight) was observed in a higher percentage of subjects treated with brexpiprazole compared with placebo, both in short term controlled trials (9.1% in the brexpiprazole 2 to 4 mg/day group vs 3.8% PBO) and in the Double-blind Maintenance phase of the long term controlled trial 331-10-232 (5.2% vs 1.0%). At the end of the Stabilization phase of study 331-10-232 a ≥ 7% increase in body weight was reported for 25/202 subjects (12.4%). The incidence of PCR weight increase (increase of ≥7% from baseline in body weight) in the fixed-dose trials showed a trend towards dose dependency (4.4%, 7.2%, 9.1% and 8.4% in the brexpiprazole 0.25 mg/day, 1 mg/day, 2 mg/day, and in the brexpiprazole 4 mg/day groups respectively, compared with 3.3% in the placebo group and 12% in the >4 mg group in short term trials. In the long term open label trials, 20.7% of subjects had a weight increase that met the PCR criterion (increase of ≥7% from baseline in body weight). In short term controlled trials, the incidence of PCR weight increase (increase of ≥7% from baseline in body weight) in the 2-4 mg group (9.1%) was higher than the one observed with aripiprazole (4%) and lower than the one observed with quetiapine (16.3%), even though the limited number of patients included in the groups treated with active comparators should be taken into account in the interpretation of these data.
Weight increase by time period showed a tendency towards an increased incidence over time (1.96%, 2.24%, 3.31%, 3.89 % at onset time intervals < 8 weeks; ≥ 8 weeks but < 14 weeks; ≥ 14 weeks but < 26 weeks; ≥26 weeks but < 52 weeks). In long term open label trials, the incidence of subjects with TEAEs of weight increased was higher in the population of subjects who completed 52-weeks of treatment (12.5% of completers vs 8.5% of safety sample) than in the pooled population that included subjects who were treated for a shorter time period. In long term open label trials -in the subjects who had a weight gain meeting the PCR criterion (weight gain ≥7%, 20.7% of subjects at any visit)- weight increased over time, with mean weight gains of 7.0, 7.8, 9.0, 10.3, and 10.2 kg at Weeks 8, 14, 26, 38, and 52, respectively.
Due to the progressively lower number of subjects included at longer time intervals, available data do not allow to conclusively evaluate increased incidence over time of uncommon/rare TEAEs. Weight gain

is listed among important identified risks in the RMP. In the proposed SmPC weight gain is listed among ADRs in section 4.8 and in section 4.4 of the SmPC there is a warning on weight gain recommending clinical monitoring of weight and providing the information that the frequency of weight increased increases with increased exposure.

Hyperglycaemia and diabetes mellitus: In the maintenance phase of the long-term controlled trial 331-10-232, a higher frequency of patients treated with brexpiprazole (1-4 mg) experienced shifts in fasting glucose from normal to high (4.55%) and from normal or impaired (≥100 and <126 mg/dL) to high (3.8%), compared to PBO group (0 and 1.3%, respectively), and a slightly higher frequency of subjects met values of Potential Clinical Relevance in fasting glucose [20/89 (22.5%) in the brexpiprazole 1-4 mg, compared to 17/88 (19.3%) in the PBO group]. One serious TEAE of type 2 diabetes mellitus (from short term controlled study 14644A) considered by the investigator as related to IMP, occurred in a in the 2-4 mg dose group, after 20 days of brexpiprazole treatment. TEAEs related to blood glucose (including diabetes mellitus) occurred in open label long term schizophrenia trials and in ongoing MDD trial, as well as in the US post-marketing setting. Hyperglicaemia has been included as important potential risk in the RMP. A warning on hyperglycaemia and diabetes mellitus has been included in section 4.4 of the SmPC, recommending to assess fasting plasma glucose before or soon after initiation of antipsychotic medication, and monitor periodically during long term treatment.

Dyslipidemia: Treatment-emergent AEs related to lipids were reported by 8 (0.7%) subjects in the brexpiprazole 2 to 4 mg/day group and no subjects in the placebo group. One subject was discontinued from IMP because of a TEAE related to lipids (blood triglycerides increased). In the fixed-dose trials treatment emergent shifts in fasting lipids from normal at baseline to borderline/high at last visit showed a higher frequency for the 4 mg dose group compared to PBO, for fasting total cholesterol, fasting LDL and fasting triglycerides. One subject in the brexpiprazole 4 mg group presented shifts in fasting triglycerides from normal at baseline to very high (≥500 mg/dl) at last visit, compared to no such events occurring in the PBO group or with lower brexpiprazole doses. A warning on weight gain and dyslipidaemia has been included in section 4.4 of the SmPC, recommending to assess fasting lipid profile at baseline and monitor periodically weight and lipid profile during treatment. Furthermore, blood triglycerides increased are listed among ADRs in section 4.8 of the SmPC.

Extrapyramidal symptoms and akathisia are common adverse reactions of antipsychotic medications, even if atypical antipsychotics are considered to have a reduced burden of extrapyramidal symptoms and akathisia relative to the older conventional antipsychotics. In short term controlled trials, a dose-response relationship for TEAEs related to extrapyramidal symptoms was observed for brexpiprazole (4.4%, 7.2%, 9.8%, 14.3% and 24.7% in brexpiprazole dose groups 0.25 mg/day, 1 mg/day, 2 mg day, 4 mg day in fixed-dose trials and 5±1 mg day in the fixed/flexible trial 331-07-203, respectively). A frequency of EPS-related TEAEs higher than PBO (9.9%) was observed only for the higher proposed therapeutic brexpiprazole dose (4 mg). A similar pattern (dose-response relationship and frequency higher than placebo only for the higher proposed therapeutic brexpiprazole dose) was observed for the two most frequent extrapyramidal symptoms: akathisia events (0, 3.4%, 5.0%, 7,1%, 16.1% and 5.6%) and parkinsonian events (3.3%, 3.8%, 4.4%, 5.9%, 9.7% and 2.7%) in brexpiprazole dose groups 0.25 mg/day, 1 mg/day, 2 mg day, 4 mg day in fixed-dose trials and 5±1 mg day in the fixed/flexible trial 331-07-203, and PBO respectively). The incidence of subjects taking EPS medication during short term trials increased with brexpiprazole dose (2.2%, 6.7%, 8.2% and 13.5% of subjects in brexpiprazole 0.25, 1 mg, 2 mg, and 4 mg/ day groups, respectively). Four subjects (0.2%) in the short term all brexpiprazole treatment group had TEAEs associated with EPS that were considered to be severe and in eight subjects (0.4%) TEAEs associated with EPS led to discontinuation. For most

akathisia events –also in the PBO group- the time of first onset was in the category "study days 8-21". In short term controlled trials, the higher proposed therapeutic brexpiprazole dose (4 mg) seems to present a worse safety profile due to a higher frequency of extrapyramidal symptoms TEAEs compared with quetiapine (14.3% vs 9.2%) and aripiprazole (12.0%), mostly driven by a higher frequency of akathisia events (7.1% vs 3.9% and 4.0 respectively in brexpiprazole 4 mg (n= 477), quetiapine (n=153) and aripiprazole (n=50) treated patients), even though the limited number of patients in these comparator groups should be considered in the interpretation of data.
In the double-blind maintenance phase of long-term trial 331-10-32, at least one TEAEs related to EPS occurred in 6.19% (6/97) and 4.81% (5/104) of subjects in the brexpiprazole and placebo treatment groups respectively. In long-term open label trials, 11% (159/1426) of subjects experienced TEAE associated with EPS. In five of these subjects (3%) the events were serious and led to discontinuation (4 subjects) or dose reduction (1 subject). In the long-term open label trials there were two events of tardive dyskinesia. The Applicant presented also an analysis of assessments of EPS, using Extrapyramidal Symptom scales, that confirmed a trend towards a higher frequency of PCR shifts with higher brexpiprazole doses.
In section 4.8 of the proposed SmPC akathisia has been listed as common ADR and Parkinsonism has been listed as uncommon ADR; furthermore the information on the dose-response relationship for akathisia in patients treated with brexpiprazole, with an increasing frequency with higher doses has been provided.
Available data do not allow to conclude on an association between akathisia and TEAEs related to suicidality or violent behaviour in brexpiprazole-treated patients. The issue should be monitored in upcoming PSURs.

Agranulocytosis, Neutropenia, and Leukopenia: In short term controlled trials, a similar proportion of subjects experienced these TEAEs between brexpiprazole and PBO treated subjects (0.2 vs 0.4%), no such events occurred during the double blind maintenance phase of trial 331-10-232, and 6 subjects (0.42%) in the Long-term open label trials experienced TEAEs of hematopoietic/leukopenia events. In the brexpiprazole < 2 mg/day group, 1 subject (0.2%) had a TEAE of agranulocytosis. Two (2.1%) subjects in the brexpiprazole group had PCR values for WBC (one case of decrease ≤2800 and one case of increase >16.000), compared with 0 (0.0%) subjects in the placebo group. Cases of leukopenia and pancythopenia with brexpiprazole occured in the postmarketing setting (source PADER Apr 2016- July 2016, PADER Jan 2016 Apr 2016 and PADER July 2015 Oct 2015). As stated by the Applicant in the RMP, Leukopenia/neutropenia has been reported during treatment with antipsychotic agents.
Agranulocytosis (including fatal cases) has been reported with some agents in the class. Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count WBC) and history of drug induced leukopenia/neutropenia. Thus a warning on Leukopenia, Neutropenia, and Agranulocytosis has been added in section 4.4 of the SmPC, similarly to the one present in the FDA Rexulti Label ("Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC occurs in absence of other causative factors.").

Neuroleptic Malignant Syndrome: Cases of Neuroleptic Malignant syndrome occurred in brexpiprazole treated patients in the post marketing setting. Even though the limited available data do not allow to definitely conclude on the causal association with brexpiprazole in these specific cases, a causal relationship is suspected due to the known association between NMS with administration of antipsychotics. Thus Neuroleptic Malignant Syndrome has been listed in section 4.8 of the SmPC and has been added as important potential risk in the RMP. A warning regarding Neuroleptic Malignant Syndrome has been included in section 4.4 of the SmPC.

No events of serotonin syndrome were reported in the brexpiprazole CDP. The Applicant conducted a search in the safety database for postmarketing events of the PT serotonin syndrome reported with Rexulti cumulatively through 25 Jun 2017. As a result of this search 4 events of serotonin syndrome were retrieved. In all 4 cases there was a potential confounder due to concomitant antidepressant therapy.The occurrence of serotonin syndrome will be followed up in upcoming PSURs.
Orthostatic hypotension and syncope: In short term controlled trials, TEAEs of dizziness, syncope or orthostatic hypotension occurred in 2.8% of subjects in the brexpiprazole 2-4 mg/ day group and 8.6% in >4 mg group, compared with 1.5% in the placebo group. Two subjects had severe events that led to discontinuation of IMP: one serious event of dizziness (brexpiprazole 2 to 4 mg/day group) and one event of syncope (brexpiprazole > 4 mg/day group). Dizziness was the most frequent TEAE of this set of events (short term controlled trials: brexpiprazole 2-4 mg group 2.3%, >4 mg: 4.4% vs PBO 1.4%), followed by orthostatic hypotension (short term controlled trials: brexpiprazole 2-4 mg group 0.3%, >4 mg: 2.2% vs PBO 0.1%) and syncope (brexpiprazole > 4 mg/day group 1.1% vs 0 PBO). The incidence of TEAEs of dizziness, syncope or orthostatic hypotension observed in the brexpiprazole 2-4 mg group (2.8%) and in the 4 mg/ day group (3.1%) was higher than the one observed with aripiprazole (2%) and lower than the one observed with quetiapine (14.4%), even though the limited number of patients included in the groups treated with active comparators should be taken into account in the interpretation of these data. One serious event of syncope occurred in an ongoing MDD trial (331-12-282). In the US post marketing setting, 4 events of syncope were reported and three events of orthostatic hypotension (PADER 10 Jan 2016 to 9 Apr 2016, 10 July 2016 to 9 Oct 2016). Adequate information are provided to the prescriber in section in Section 4.4 of the SmPC, on Orthostatic hypotension and syncope, stating that these risks are greatest at the beginning of treatment with antipsychotics and during dose escalation and that in patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension using a lower starting dose and slower titration should be considered and orthostatic vital signs should be monitored. Dizziness is listed as ADR in section 4.8 of the proposed SmPC. Furthermore, in section 4.4 of the SmPC a warning on cardiovascular disorders has been included, on the need to use brexpiprazole with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension (including accelerated or malignant). The information that brexpiprazole has not been evaluated in patients with a history of myocardial infarction/ ischaemic heart disease or clinically significant cardiovascular disease since such patients were excluded from clinical trials has been provided to the prescribers.

Hyperprolactinaemia: Antipsychotics have been shown to elevate prolactin concentrations via dopamine D2 antagonism. In short term controlled trials, potentially Clinically Relevant Changes (PCR) in prolactin (> 1 × ULN) were more frequently observed in the brexpiprazole 2 to 4 mg/day group compared with the placebo group, particularly in females (13.7 vs 6.4% in female;11.1 vs 10.3% in males). In the Double blind Maintenance phase, where most patients were males - values for prolactin that were > 1 × ULN and > 2 × ULN were each reported for 2 (5.3%) female subjects in the brexpiprazole group and 1 (2.6%) female subject in the placebo group. The incidence of PCR prolactin elevations observed in the brexpiprazole 2-4 mg group (13.7%) and in the 4 mg/ day group (15.3%) was higher than the one observed with both aripiprazole (0) and quetiapine (8.2%), even though the limited number of patients included in the groups treated with active comparators should be taken into account in the interpretation of these data.
The frequencies of shifts from baseline with potential clinical relevance of increase for prolactin in patients with normal prolactin values at baseline, as well as mean and median changes from baseline,

showed a trend towards a dose-dependency in female patients, in fixed dose trials. In males smaller changes were observed, with smaller differences from placebo. From available data, frequencies of prolactin increases from baseline PCR in female patients with normal prolactin at baseline tended to be higher in long term uncontrolled trials compared to those observed in short term trials.
Treatment-emergent AEs related to prolactin (blood prolactin increased, blood prolactin decreased, or hyperprolactinemia) were reported in 2.2% (n=17) in the 2-4 mg brexpiprazole-treated groups, 2.2% (n=2) in the >4 mg group and in 1.1% (8 subjects) in the placebo group. All of these TEAEs were considered mild or moderate in severity by the investigator. The dose of IMP was not changed for any of these subjects due to the increase in prolactin. Five of these subjects had a prolactin level > 3 × ULN. A search of the clinical database for TEAEs in the SOCs of Reproductive System and Breast Disorders and Psychiatric Disorders (sexual function-related AEs; eg, decreased libido, anorgasmia) for the 22 subjects with TEAEs related to prolactin revealed that they had none of these types of TEAEs in these SOCs. In short term controlled trials among subjects with potentially clinically relevant changes (PCR) in prolactin (> 1 × ULN), one patients each in brexpiprazole and PBO group experienced dysmenorrea and no subjects experienced sexual function related TEAEs. In long term trials among subjects with potentially clinically relevant changes (PCR) in prolactin (> 1 × ULN) one patient presented a TEAE of menstruation irregular and one patient presented a TEAE of libido decreased. The event was mild in severity and was considered possibly related to the study drug. In the short-term trials, TEAEs in the SOC reproductive system and breast disorders (including erectile dysfunction, breast tenderness and galactorrhea) were reported in 1.6% of subjects in the 2-4 mg brexpiprazole group, 2.2% in the >4 mg group, compared to 0.7% in PBO. In long term open label trials, treatment-emergent AEs related to prolactin were reported in 23 subjects (1.6%) (hyperprolactinaemia: 9 subjects; blood prolactin decreased: 1 subject; blood prolactin increased 13 subjects). In long term open label trials 3 events of libido decreased (SOC Psychiatric disorders), 3 events of menstrual disorders, 2 events of menstruation irregular, 1 event each of breast discomfort, galactorrhea and hypomenorrhea occurred. In an ongoing MDD trial (331-12-282), two serious TEAEs of breast cancer and intraductal proliferative breast lesion occurred. Through US post-marketing experience (Cut-off date October 2016), 5 events of prolactin increased/hyperprolactinaemia and 8 events of galactorrhoea have been reported, in addition to other reported events of reproductive and breast disorders (e.g. gynecomastia 2 events, sexual dysfunction 2 events, female breast cancer 1 event, amenorrhoea 1 event) that may be induced by hyperprolactinemia. Also in light of nonclinical evidences, the available data do not allow to definitely conclude on the relevance of clinical consequences of hyperprolactinaemia. A warning has been included in section 4.4 on the occurrence of hyperprolactinaemia, and hyperprolactinaemia and related disorders have been classified as important potential risk in the RMP. Blood prolactin increased has been listed as very common ADR in section 4.8 of the SmPC.

QT prolongation: Prolongation of QT interval is a class effect for atypical antipsychotics. In the Thorough QT Trial 331-10-242, the by gender subgroup analysis showed significant results (upper bound CI > 10 msec) in female subjects both at therapeutic (4 mg) e sovratherapeutic (12 mg) brexpiprazole doses (see PK section for details). In the Applicant's opinion the observed differences between genders were most likely related to the smaller number of female than male subjects in each treatment group (14 females versus 48 males for brexpiprazole 4 mg, 13 versus 40 for brexpiprazole 12 mg, and 13 versus 50 for moxifloxacin). In Short term controlled trials, within the proposed therapeutic 2-4 mg dose, the incidence of TEAEs related to QT prolongation was comparable between brexpiprazole (0.3%) and placebo (0.5%), while a higher frequency was observed in the brexpiprazole > 4 mg group (3.2%) groups. Also regarding frequencies of categorical changes in QT, frequencies higher than in PBO were observed only in the brexpiprazole >4 mg group (QTcF ≥ 450 msec 4.4% vs 2.9%; increase in QTcF interval of ≥ 60 msec: 1.1% vs 0.1%) and for the 2-4 g dose only for increase in QTcF interval of ≥ 60

msec: 0.3% vs 0.1%). Available data on frequencies of categorical changes in QT by dose up to 4 mg dose in fixed-dose short-term controlled trials do not show dose dependency in QTcB or QTcF increases in brexpiprazole treated patients. In long-term open label trials a new onset QTcF interval over 500 msec and new onset QTcB intervals over 500 msec were each reported in 1 (0.1%) subject (both prolongations were in Subject), compared to no QTc interval increases over 500 ms in short term controlled trials; a total of 7 subjects (0.5%) had a TEAE related to QT prolongation. There were 8 TEAEs of ECG QT prolonged in 7 subjects. All were considered related to IMP. Two subjects were withdrawn from IMP. An elderly subject with MDD (Subject, treated with brexpiprazole) was discontinued from IMP due to a TEAE of electrocardiogram QT prolonged that was assessed as related to IMP. In long term controlled trial 331-10-232 the incidence of increases of QTcB > 60 msec was 3.2% (3 subjects) in the brexpiprazole group compared with 1.0% (1 subject) in the placebo group. With regard to the post marketing experience of QT prolongation with brexpiprazole, a search conducted in the Applicant's safety database for post marketing events of electrocardiogram QT prolonged reported with Rexulti cumulatively through 25 Jun 2017 retrieved 3 events. Of these, one was reported as serious and one led to withdrawal. The post-marketing cases of electrocardiogram QT prolonged each present limited information with confounding histories of cardiac events and concomitant medications, co-suspect medication, or unknown medical and past drug histories. On the basis of the above, QT prolongation has been added in section 4.8 of the SmPC (frequency unkown). A warning on QT prolongation has been included in section 4.4 of the SmPC on the need to exercise caution when brexpiprazole is prescribed in patients with known cardiovascular disease or family history of QT prolongation, electrolyte imbalance, and in concomitant use with other medicinal products thought to prolong the QT interval, with cross reference to section 4.8 and 5.1. In section 4.8 of the SmPC, the information that subgroup analyses from the thorough QTc trial suggested that the QTc prolongation was larger in female subjects than in males has been provided to prescribers, with cross reference to section 5.1.

Creatine Phosphokinase Elevation and Rhabdomyolysis: In short term controlled trials, in the all brexpiprazole treatment group, 7.7% of subjects had a PCR CPK value (≥3 x ULN), compared with 5.5% in the placebo group. During the Double blind Maintenance phase of trial 331-10-232, the incidence of PCR changes in CPK (≥ 3 × ULN) was lower in the brexpiprazole group (1 subject [1.1%]) compared with the placebo group (4 subjects [4.0%]). In the long-term, open-label trials, a total of 109 subjects (8.1%) had PCR CPK test results (≥ 3 × ULN); among these, 44 subjects (3.1%) had a PCR CPK value ≥ 5 × ULN, 27 subjects (1.9%) had a PCR CPK ≥ 7 × ULN, and 12 subjects (0.8%) had a PCR CPK ≥ 10 × ULN. Blood creatinine phosphokinase increased has been included in the Table of ADRs in section 4.8 of the SmPC. In section 4.5 (Interaction with other medicinal products and other forms of interaction) the information that, in case of co-administration with drugs known to increase CPK, the possible additive effect with CPK increase induced by brexpiprazole should be considered has been provided to prescribers.
Rhabdomyolysis is a known class effect of antipsychotics. At least one event of rhabdomyolysis possibly related to brexpiprazole occurred in brexpiprazole CDP and at least one further event for which a causal relationship with brexpiprazole may not be excluded occurred in the post-marketing section. Thus rhabdomyolysis has been added in section 4.8 of the SmPC.

Seizures: The frequency of seizures related TEAEs was similar in short term controlled trial, between the 2-4 mg brexpiprazole dose group and placebo (2 subjects in each group, 0.16% vs 0.27%); a (Patient, from study 14644A) -with no relevant medical history- experienced a serious event, severe in intensity, of grand mal convulsion, leading to withdrawal from the study, 4 days after the first dose of brexpiprazole 4 mg. In long term controlled trial 331-10-232 one event of convulsion was reported in a

subject treated with brexpiprazole 4 mg. Two events of seizures (one serious) occurred in long term, open label trials, both leading to withdrawal. Seizures have been listed as ADRs in Section 4.8 of the SmPC, based on the observations of seizures both in animal and human studies, and the fact that seizure is a known class effect attributed to antipsychotics.

Somnolence: The TEAEs related to somnolence (hypersomnia, sedation, and somnolence) showed a dose relationship with higher frequencies observed with higher doses (1.1%, 2.6%, 3.1%, 4.6% in the brexpiprazole 0.25, 1, 2 mg/day and 4 mg/day short term fixed dose groups and 10.8% in the >4 mg/day short term controlled trials). The incidence of somnolence events was higher in the 4 mg/day brexpiprazole group, compared to placebo group (4.6% vs 2.9%). The incidence of TEAEs related to somnolence with brexpiprazole was comparable to the one observed with aripiprazole (4.0%) and lower compared to the one observed with quetiapine (26.1%), even though the limited number of patients included in the groups treated with active comparators should be taken into account in the interpretation of these data. There were no serious TEAEs related to somnolence and no subject discontinued from IMP due to a TEAE related to somnolence. With the exception of one event of severe sedation, all other TEAEs related to somnolence were mild or moderate in severity. There were no reports of somnolence, hypersomnia, or sedation within the Nervous System Disorders SOC in any treatment group during the Double blind Maintenance phase of trial 331 10 232. A TEAE related to somnolence was reported by 60 subjects (4.2%) in the long-term open-label trial. One subject was discontinued from IMP due to a TEAE related to somnolence. There was 1 serious TEAE related to somnolence. The dose of IMP was not changed and the event resolved. In section 4.8 of the SmPC sedation is listed as common ADR.

Suicidality: In short-term, controlled Trials, TEAEs related to suicidality were reported by 8 subjects (0.5%, 2 serious events, 1 leading to discontinuation) in the all brexpiprazole treatment group and 3 subjects (0.4%, none serious) in the placebo group. In long-term, Open-label Trials, TEAEs related to suicidality were reported for 23 subjects (1.6%). In Brexpiprazole CDP, one death due to suicide occurred in schizophrenia trials, considered not drug related by the investigator, and 2 deaths due to suicide occurred in MDD trials; one of these case was considered possibly related by the investigator. Spontaneous cases reporting completed suicide and suicide attempt were reported in the postmarketing setting. Suicidal ideation and suicidal attempt have been listed as uncommon ADRs in section 4.8 of the SmPC. In section 4.4 of the proposed SmPC, a warning related to Suicidality has been included.
Since non-clinical and clinical data available at the time of the initial marketing authorisation do not allow to rule out a possible association between hypothermia and brexpiprazole administration, hypothermia should be monitored in upcoming PSURs. Hypothermia should be monitored in upcoming PSURs.

In controlled schizophrenia clinical trials, no deaths occurred in the PBO arm, compared with three deaths (0.1%) in brexpiprazole arms; one found dead 12 days after the end of a 6 weeks brexpiprazole trial, cause of death unknown; for the other two cases of death there were confounding factors/ alternative explanations (12 days after the end of a 6 weeks brexpiprazole trial;). Other 6 deaths occurred in schizophrenia open-label trials, all considered not drug related by the investigators (gastric ulcer perforation/peritonitis: , with no confounding factors, treated with brexpiprazole 2 mg, uterine cancer in a treated with brexpiprazole 4 mg/ day; for the other cases of death -septic shock, cardiac failure, coronary artery disease, completed suicide- there were possible confounding factors). In MDD trials no deaths occurred during the controlled treatment period, while 7 subjects died during the long term open label brexpiprazole trials (2 cases of completed suicide; one case each of: metastatic

malignant melanoma, pulmonary embolism, gastric ulcer perforation/peritonitis , ovarian cancer, acute myocardial infarction/ myocardial rupture), all considered not drug related by the investigator, apart from one case of completed suicide considered possibly related; for all the 7 cases of death possible confounding factors were in place.
Other Serious AEs occurred with similar frequencies in short term controlled schizophrenia trials between brexpiprazole (3.4%) and placebo (4.2%). The serious TEAEs reported by more than 1 subject in the brexpiprazole 2 to 4 mg/day group were predominately in the Psychiatric Disorders SOC, including schizophrenia and psychotic disorder.
Concerning laboratory findings, due to the higher frequency in brexpiprazole treated subjects compared to PBO in the maintenance phase of long term controlled trial 331-10-232 of ALT and AST increased, of TEAEs associated with hepatic function, and of discontinuation due to TEAEs related to hepatic function in long term controlled trial 331-10-232, hepatic enzyme increased has been listed as ADR in section 4.8 of the SmPC.
Only 5 subjects aged ≥65 years were included in short term controlled trials. No subject aged ≥63 years old was enrolled in the long-term, Controlled Trial 331-10-232. In long term open label trials only 30 subjects aged ≥65 years old were enrolled. Elderly patients are expected to have a worse safety profile with antipsychotics. Per clinical trials inclusion criteria, only patients up to 65 years of age were included in clinical trials. Available data do not allow to assess brexpiprazole safety in schizophrenic elderly patients. Adequate information has been provided to prescribers in the SmPC.
The information on the higher frequency of vomiting and nausea observed in females compared to males in short term trials should be added in section 4.8 of the SmPC, with cross reference to section 5.2 of the SmPC, where the information on the higher exposure (AUC) of brexpiprazole in women is provided.
In short term controlled schizophrenia trials TEAEs corresponding to PTs in the SMQ of gastrointestinal perforation, ulceration, haemorrhage or obstruction occurred with similar frequency between brexpiprazole treated subjects (8/1748, 0.45%) and PBO (2/740, 0.3%), with one serious event in each group. In long term open label schizophrenia trials, 9 events of gastrointestinal disorders were reported. Among these, 4 serious events including one with fatal outcome were identified. None of these events were assessed as related to the study drug by the Investigator. One fatal event of gastric ulcer was reported in the long term open label MDD study trial 331-10-238, considered by the Investigator not to be related to study treatment. Available data do not allow to conclude on a causal association between brexpiprazole treatment and gastric ulcers; the occurrence of gastrointestinal haemorrhage during brexpiprazole treatment should be monitored in upcoming PSURs.

2.1.2. Conclusions on the clinical safety

The overall exposure to the drug has been relatively extensive, especially taking into account post-marketing experience.
Brexpiprazole safety appears overall in line with known antipsychotic class effects. Data from clinical studies clearly indicate that brexpiprazole treatment is associated with weight gain, extrapyramidal symptoms -including akathisia-, hyperprolactinaemia, CPK increase, dizziness and sedation.
The Applicant provided a comparison of safety data available for brexpiprazole with data available for other antipsychotics, using both data coming from US product labels and published data. Despite the limitations of the indirect comparison (for instance different definitions of EPS related TEAE were used and safety data from different dose ranges for each antipsychotic were pooled together), from the available data brexpiprazole compared with aripiprazole appears to have a lower frequency of sedating AEs and insomnia, a similar frequency of akathisia and EPS adverse events and a higher frequency of long term weight gain. A dose-dependency was observed in the frequency of the following TEAEs:

akathisia (3.4%, 5.0%, 7.1%, respectively in brexpiprazole 1 mg, 2 mg and 4 mg; compared to 5.6% in PBO), parkinsonism (3.8%, 4.4%, 5.9% respectively in brexpiprazole 1 mg, 2 mg and 4 mg; compared to 2.7% in PBO) and somnolence (2.6%, 3.1%, 4.6%, respectively in brexpiprazole 1 mg, 2 mg and 4 mg; compared to 2.9% in PBO). Weight gain increases with increased exposure.

Brexpiprazole appears to offer no clear advantages over other newer 2nd generation antipsychotics in terms of the common safety issues associated with this class of drug e.g. motor effects (EPS) or metabolic effects; however indirect evidences suggest a lower risk of sedation compared to other antipsychotics. No new and unexpected safety signals have been identified with brexpiprazole, but no robust direct evidence has been provided to support any claims of improved safety, compared to other similar partial agonist antipsychotics, either.

2.2. Risk Management Plan

Safety concerns

Important Identified Risks	Weight gain
Important Potential Risks	Hyperglycaemia Neuroleptic malignant syndrome Hyperprolactinaemia and related disorders
Missing Information	Use in pregnancy and lactation Use in elderly (age > 65) Substance abuse, misuse, and overdose Use in patients with insulin dependent diabetes mellitus (IDDM).

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities				
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation – Not applicable				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances - Not applicable				
Category 3- Required additional pharmacovigilance activities				
Study and Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Data collection from participation in the Pregnancy	Primary: To prospectively evaluate rates of congenital malformations among infants exposed in utero to psychiatric	Missing Information: Use in pregnancy and	Periodic updates	Data will be reviewed on an ongoing basis as it is provided to the Applicant as per associated published literature, and utilized in

Ongoing and Planned Additional Pharmacovigilance Activities				
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation – Not applicable				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances - Not applicable				
Category 3- Required additional pharmacovigilance activities				
Study and Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Registry - NPRAA Ongoing (category 3)	medications Secondary: 1) To evaluate neonatal outcomes of infants with prenatal exposure to specific psychiatric medications alone or in combination with other psychotropics 2) To evaluate maternal health outcomes associated with use of psychiatric medication during pregnancy 3) To evaluate neurobehavioral development of children (1 month and older) with prenatal exposure to atypical antipsychotics	lactation		signal detection and provided in the PBRER/ PSUR when available.

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Weight gain	Routine risk minimisation measures: • SmPC Sections 4.4, 4.8 • PIL Sections 2, 4 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Hyperglycaemia	Routine risk minimisation measures: • SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	• PIL Section 2 • Prescription only medicine.	Additional pharmacovigilance activities: None.
Neuroleptic malignant syndrome	Routine risk minimisation measures: • SmPC Sections 4.4, 4.8 • PIL Sections 2, 4 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Hyperprolactinaemia and related disorders	Routine risk minimisation measures: • SmPC Sections 4.4, 4.8 • PIL Sections 2, 4 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in pregnancy and lactation	Routine risk minimisation measures: • SmPC Sections 4.6, 5.3 • PIL Section 2 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Data collection from participation in the NPRAA
Use in elderly (age >65)	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, 5.2 • PIL Section 2 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Substance abuse, misuse, and overdose	Routine risk minimisation measures: • SmPC Section 4.9 (overdose) • PIL Section 3 (overdose) • Limited pack sizes to restrict access for potential misuse • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Use in patients with Insulin dependent diabetes mellitus (IDDM)	Routine risk minimisation measures: • SmPC Section 4.4 • PIL Section 2 • Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 (dated 20 April 2018) is acceptable.

2.3. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

The summary includes the following elements:

· Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance

· The Member States in which the qualified person resides and carries out his/her tasks

· The contact details of the qualified person

· A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC

· A reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 10th July 2015. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.4. New Active Substance

The applicant compared the structure of brexpiprazole with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers brexpiprazole to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.5. Product information

2.5.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.5.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, RXULTI (brexpiprazole) is included in the additional monitoring list as per the following reason:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Brexpiprazole is intended for the treatment of schizophrenia in adults. Schizophrenia is a severely debilitating psychotic disorder; symptoms are classified as so-called positive (delusions, hallucinations, disorganised speech, and disorganised or catatonic behaviours) and negative (affective flattening, restriction in the fluency and productivity of thought and speech and in the initiation of goal directed behaviour). In addition, cognitive deficits are common. The positive symptoms appear to reflect an excess or distortion of normal functions, whereas negative symptoms reflect a diminution or loss of normal function. A patient usually gradually recovers from the first episode of schizophrenia. However, relapses are common, and pattern of the illness during the first 5 years indicates generally the course. The aim of therapy is to treat acute episodes and control symptoms in the long term preventing further relapses.

3.1.2. Available therapies and unmet medical need

Antipsychotic medications are the mainstay treatment for schizophrenia in addition to psychosocial interventions. Antipsychotics diminish symptoms and reduce relapse rates. Antipsychotics have a wide variety of pharmacological properties but they all have a capacity to antagonize postsynaptic dopamine receptors in the brain. Only 10-20% of schizophrenia patients have been described to achieve a good outcome. It has been estimated that 20-30% continue to experience moderate symptoms and 40-60% remain significantly impaired. Second-generation (atypical) antipsychotics (SGAs) are the agents of choice for first-line treatment of schizophrenia. Clozapine is not recommended because of its risk of agranulocytosis. SGAs are usually preferred over first-generation (typical) antipsychotics (FGAs) because they are associated with fewer extrapyramidal symptoms. However, SGAs tend to have metabolic side effects, such as weight gain, hyperlipidemia, and diabetes mellitus. Since adverse effects can contribute to the increased risk of cardiovascular mortality observed in schizophrenia patients. The hypothetical expectations of brexpiprazole's benefit in treating schizophrenia has been based on its receptor profile and similarities with aripiprazole. Brexpiprazole is expected to have an efficacy comparable with currently available SGAs and a more favourable side effects profile, with less EPSs and metabolic adverse events.

3.1.3. Main clinical studies

Efficacy of brexpiprazole was studied in three 6 weeks, fixed-dose, placebo-controlled pivotal trials (331-10-**231** and 331-10-**230)**, one of which is a regional study conducted in Japan (331-10-**002**). In

addition, another pivotal study was a six-weeks, flexible-dose study with active reference quetiapine (**14644A**). A 6-weeks dose-finding study with active reference aripiprazole was also conducted (**203**). A relapse prevention study with a randomized withdrawal phase was conducted to assess long-term maintenance efficacy of brexpiprazole in schizophrenia (331-10-**232**).
Each of the three fixed-dose trials investigated the efficacy and safety of the dose of 2mg/day and 4mg/day, but also had a lower dose arm. With the exception of the 002 regional study, the randomization was imbalanced with fewer patients in the lower doses arms. In the 231 study the lower dose was 0.25mg (3:3:2:3 randomization), in the 230 study the lower dose was 1mg (2:2:1:2 randomization) and in the 002 trial the lower dose was 1mg (1:1:1:1 randomization).
The titration scheme differs between the fixed dose trials (maximum dose of 4 mg is reached in 7 days) and the flexible dose trial (maximum dose of 4mg/day is reached in 4 days). In the latter, the titration scheme is faster to allow a comparison with the established quetiapine titration scheme.
All 4 short term trials have the same primary endpoint which is "change from baseline to week 6 in the PANSS total score". The PANSS is an established and clinically meaningful endpoint and the choice of the same primary outcome measure for all trials allows comparability. As per Guidelines the CGI-S scale was chosen as a key secondary endpoint to allow assessment of clinical meaningfulness.
Trial 331-10-**232** is a multicentre double blind placebo controlled relapse prevention trial to assess the efficacy safety and tolerability of brexpiprazole (1 to 4mg/day) as maintenance treatment in adult patients with schizophrenia. The trial consisted of a screening period during which eligibility criteria were assessed; a period for conversion from other antipsychotic(s) to oral brexpiprazole and washout of prohibited concomitant medications, if applicable; a single-blind treatment phase to stabilize subjects on oral brexpiprazole; a double-blind randomization phase to assess maintenance of effect, and a post-treatment follow-up for safety monitoring. The primary efficacy endpoint of this trial was the time from randomization to impending relapse.
All trials, with the exception of study 202 (Japan) enrolled also patients from the EU.

3.2. Favourable effects

The first pivotal phase 3 study (331-10-**231**) supports efficacy of brexpiprazole at the doses of 2 and 4 mg/day in terms of reduction of symptoms as measured by the PANSS. The mean reduction of PANSS total score at week 6 was -20.73 for the group treated with 2mg and was -19.65 for the group treated with 4mg, therefore the separation from placebo (LS mean -12) was statistically significant ($p<0.0001$ and $p=0.0006$, respectively). Patients treated with the dose of 0.25 improved minimally (LS mean change from baseline -14.90), although the power calculated for the 0.25 arm was less than 70% (imbalanced randomization). Efficacy is also supported by the results at the key secondary endpoint change from baseline to week 6 in the CGI-S score. The LS mean of the brexpiprazole 2mg treatment arm was -1.20 therefore the separation from placebo was statistically significant ($p=0.0056$), the same applies for the 4mg treatment arm (LS mean -1.15), which separated significantly from placebo ($p=0.0012$). Patients treated with the dose of 0.25 improved minimally (LS mean change from baseline -0.85).
The second phase 3 short term pivotal study (331-10-**230**) supports an effect of brexpiprazole in reducing schizophrenia symptoms as measured by the PANSS but only at the dose of 4 mg. During the trial, patients on brexpiprazole 4mg improved significantly after 6 weeks as compared to placebo patients (LS mean -20 points; -13.53, respectively). The groups treated with the dose of 1mg and 2 mg showed similar numeric improvement (-16.9, -16.6 respectively) despite this being not statistically significant. The onset of efficacy, when measured at the PANSS, was already significant at week 1, but only in the 4 mg arm. The difference in CGI-S scores between treatment and placebo showed a similar pattern where only patients in the 4mg arm separated significantly from placebo (-1.19 LS mean vs

-0.81 treatment and placebo respectively). Numeric improvement in the 2mg and 1mg arms was similar.
In the regional phase 3 study (331-10-**002**) results support the efficacy of brexpiprazole in reducing schizophrenia symptoms as measured by the PANSS but only at the dose of 2 mg. The group treated with 2 mg improved substantially (LS mean change -14.95, p=0.0124). This difference appeared at week 3 of treatment and remained trough the study period. The group treated with 4 mg improved less (-3.86 difference from placebo, not statistically significant). The lowest numerical improvement was observed in the group treated with 1mg. Analyses of the CGI-S showed no significant difference from placebo. In a clinical perspective, it is noted that the analyses of secondary outcomes shows an effect on the negative symptoms domain, both at the PANSS negative subscale (LS mean was −3.48 in the 2 mg group and −3.24 in the 4 mg group, vs −1.20 in the placebo group) and at the Marder factor score negative symptoms where the 2 and 4 mg groups separated from placebo; the 2 mg group separated from placebo also in the disorganized though Marder factor. In the positive symptom factor there was no separation from placebo.
In the flexible dose, active and placebo controlled study **14644A,** the group treated with the dose range of 2-4 mg brexpiprazole failed to separate from placebo at the primary endpoint. Placebo patients showed a mean reduction in PANSS total scores at week 6 of -15.9 (the highest placebo response of all trials), therefore the improvement with brexpiprazole (LS mean change -20) was not sufficient to achieve statistical difference, whilst patients treated with flexible doses of quetiapine XR improved on average by -24 points therefore this different was statistically significant in comparison to placebo. When measuring the differences in reduction of PANSS total scores between the brexpiprazole group and the placebo group at weeks 2, 3 and 4, the difference was statistically significant, confirming an onset of therapeutic effect at week two, like most antipsychotics. The difference in CGI-S scores between the brexpiprazole group and placebo was statistically significant (LS mean -1.2 vs -0.9 for placebo, p=0.0142), although the numeric improvement was slightly inferior to that of the quetiapine group (LS mean -1.4, p=0.0002). A responder analysis of trial 14644A used relative risk to demonstrate that both quetiapine and brexpiprazole differentiated from placebo for reduction in PANSS scores of ≥30% and ≥ 40% but not ≥50% which fails for both active treatments.
The relapse prevention trial (331-10-**232**), was stopped at the first interim analysis for demonstration of efficacy. Indeed, relapse was significantly delayed in the brexpiprazole group as compared to placebo (p=0.0008) and subjects treated with brexpiprazole had 66% lower risk of experiencing impending relapse compared to placebo.

3.3. Uncertainties *and limitations about favourable effects*

A limitation in the assessment of efficacy comes from the fact that the two active comparator studies 203 (a dose finding study) and 14644A were negative. While in study 203 neither brexpiprazole, or aripiprazole separated from placebo, in study 14644A assay sensitivity was demonstrated and in all comparisons, including the sensitivity analyses, the magnitude of PANSS scores reduction was greater for the quetiapine group than for the brexpiprazole group. In this study the dosing regimen was flexible more representative of the proposed dosing regimen. Due to this difference, the results from this study cannot be integrated into pooled analyses or meta-analyses with the results from other short term studies.
Despite the evidence of a reduction in the PANSS scores with the 4 mg dose and also with the 2 mg dose of brexpiprazole, data do not allow a comparison with currently available treatments, other SGAs or aripiprazole. It is not possible to state if the efficacy of brexpiprazole is comparable to that of other SGAs. The only evidence points towards a smaller effect as compared to quetiapine.

3.4. Unfavourable effects

As of the data cut-off date, 3450 subjects with schizophrenia have been exposed to brexpiprazole. In the entire brexpiprazole CDP, 7020 subjects in phase 2/3 trials (for MDD, schizophrenia, ADHD, and PTSD) and 877 subjects in clinical pharmacology trials have been exposed to at least 1 dose of brexpiprazole in clinical trials conducted in North America, Latin America, Europe, and Asia.

The clinical pharmacology trials conducted in the brexpiprazole CDP include diverse populations (male and female subjects, healthy subjects, subjects with psychiatric diseases [including schizophrenia, MDD, and ADHD], subjects with hepatic or renal impairment, and limited numbers of elderly subjects), different trial designs, and doses ranging from 0.2 mg/day to 12 mg/day (1 mg/day to 12 mg/day for schizophrenia).

Brexpiprazole safety appears overall in line with known antipsychotic class effects. Data from clinical studies clearly indicate that brexpiprazole treatment is associated with weight gain, extrapyramidal symptoms -including akathisia-, hyperprolactinaemia, CPK increase, dizziness and sedation. The safety profile of the highest recommended dose (4 mg) appears worse compared with lower brexpiprazole doses.

Weight gain ≥7% from baseline occurred with a considerable higher frequency in long term open label trials (20.7%) compared to short term trials (9.1%). In long term open label trials -in the subjects who had a weight gain meeting the PCR criterion (weight gain ≥7%, 20.7% of subjects at any visit)- weight increased over time, with mean weight gains of 7.0, 7.8, 9.0, 10.3, and 10.2 kg at Weeks 8, 14, 26, 38, and 52, respectively.

In long term controlled maintenance trials, shifts in fasting glucose from normal to high occurred in 4.5% of BRX treated subjects compared to no such shifts in PBO. TEAEs related to blood glucose (including diabetes mellitus) occurred in open label long term schizophrenia trials, in an ongoing MDD trial, and in the US post-marketing setting. In short term trials, one serious TEAE of type 2 diabetes mellitus considered by the investigator as related to IMP, occurred in a, 20 days after the first BRX dose.

Treatment-emergent AEs related to lipids were reported by 8 subjects (0.7%) in the brexpiprazole 2 to 4 mg/day group and no subjects in the placebo group. One subject was discontinued from IMP because of a TEAE related to lipids (blood triglycerides increased). In the fixed-dose trials treatment emergent shifts in fasting lipids from normal at baseline to borderline/high at last visit showed a higher frequency for the 4 mg dose group compared to PBO, for fasting total cholesterol, fasting LDL and fasting triglycerides. One subject in the brexpiprazole 4 mg group presented shifts in fasting triglycerides from normal at baseline to very high (≥500 mg/dl) at last visit, compared to no such events occurring in the PBO group or with lower brexpiprazole doses.

In short term controlled trials, a dose-response relationship for TEAEs related to extrapyramidal symptoms was observed for brexpiprazole (4.4%, 7.2%, 9.8%, 14.3% and 24.7% in brexpiprazole dose groups 0.25 mg/day, 1 mg/day, 2 mg day, 4 mg day in fixed-dose trials and 5±1 mg day in the fixed/flexible trial 331-07-203, respectively). A frequency of EPS-related TEAEs higher than PBO (9.9%) was observed only for the higher proposed therapeutic brexpiprazole dose (4 mg). A similar pattern (dose-response relationship and frequency higher than placebo only for the higher proposed therapeutic brexpiprazole dose) was observed for the two most frequent extrapyramidal symptoms: akathisia events (0, 3.4%, 5.0%, 7,1%, 16.1% and 5.6%) and parkinsonian events (3.3%, 3.8%, 4.4%, 5.9%, 9.7% and 2.7%) in brexpiprazole dose groups 0.25 mg/day, 1 mg/day, 2 mg day, 4 mg day in fixed-dose trials and 5±1 mg day in the fixed/flexible trial 331-07-203, and PBO respectively). The incidence of subjects taking EPS medication during short term trials increased with brexpiprazole dose (2.2%, 6.7%, 8.2% and 13.5% of subjects in brexpiprazole 0.25, 1 mg, 2 mg, and 4 mg/ day groups, respectively). Four subjects (0.2%) in the short term all brexpiprazole treatment group had TEAEs associated with EPS that were considered to be severe and in eight subjects (0.4%) TEAEs

associated with EPS led to discontinuation. For most akathisia events –also in the PBO group - the time of first onset was in the category "study days 8-21". In the double-blind maintenance phase of long-term trial 331-10-32, at least one TEAEs related to EPS occurred in 6.19% (6/97) and 4.81% (5/104) of subjects in the brexpiprazole and placebo treatment groups respectively. In long-term open label trials, 11% (159/1426) of subjects experienced TEAE associated with EPS. In five of these subjects (3%) the events were serious and led to discontinuation (4 subjects) or dose reduction (1 subject). In the long-term open label trials dyskinesia occurred in 1.2% of subjects, with two events of tardive dyskinesia occuring in subjects exposed in the time interval >=52 weeks (2/458).
Cases of Neuroleptic Malignant syndrome occurred in brexpiprazole treated patients in the post marketing setting (source PADER July 2016 – Oct 2016, PADER Jan 2016 Apr 2016).
Hyperprolactinaemia: In short term controlled trials, potentially Clinically Relevant changes (PCR) in prolactin (> 1 × ULN) were more frequently observed in the brexpiprazole 2 to 4 mg/day group compared with the placebo group, particularly in females (13.7 vs 6.4% in female; 11.1 vs 10.3% in males). In the Double blind Maintenance phase, where most patients were males- values for prolactin that were > 2 × ULN were reported for 2 (5.3%) female subjects in the brexpiprazole group and 1 (2.6%) female subject in the placebo group. Cases of reproductive and breast disorders that may be induced by hyperprolactinemia (e.g. erectile dysfunction, breast tenderness, galactorrhea, gynecomastia, breast cancer) occured in subjects treated with brexpiprazole either in short term trial or in post marketing experience.
CPK increase: In short term controlled trials, in the all brexpiprazole treatment group, 7.7% of subjects had a PCR CPK value (≥3 x ULN), compared with 5.5% in the placebo group. During the Double blind Maintenance phase of trial 331-10-232, the incidence of PCR changes in CPK (≥ 3 × ULN) was lower in the brexpiprazole group (1 subject [1.1%]) compared with the placebo group (4 subjects [4.0%]). In the long-term, open-label trials, a total of 109 subjects (8.1%) had PCR CPK test results (≥ 3 × ULN); among these, 44 subjects (3.1%) had a PCR CPK value ≥ 5 × ULN, 27 subjects (1.9%) had a PCR CPK ≥ 7 × ULN, and 12 subjects (0.8%) had a PCR CPK ≥ 10 × ULN.
In short term controlled trials, TEAEs of dizziness, syncope or orthostatic hypotension occurred in 2.8% of subjects in the brexpiprazole 2-4 mg/ day group and 8.6% in >4 mg group, compared with 1.5% in the placebo group. Two subjects had severe events that led to discontinuation of IMP: one serious event of dizziness (brexpiprazole 2 to 4 mg/day group) and one event of syncope (brexpiprazole > 4 mg/day group). Dizziness was the most frequent TEAE of this set of events (short term controlled trials: brexpiprazole 2-4 mg group 2.3%, >4 mg: 4.4% vs PBO 1.4%), followed by orthostatic hypotension (short term controlled trials: brexpiprazole 2-4 mg group 0.3%, >4 mg: 2.2% vs PBO 0.1%) and syncope (brexpiprazole > 4 mg/day group 1.1% vs 0 PBO). One serious event of syncope occurred in an ongoing MDD trial (331-12-282). In the US post marketing setting, 4 events of syncope were reported and three events of orthostatic hypotension (PADER 10 Jan 2016 to 9 Apr 2016, 10 July 2016 to 9 Oct 2016).
TEAEs related to somnolence (hypersomnia, sedation, and somnolence) showed a dose relationship with higher frequencies observed with higher doses (1.1%, 2.6%, 3.1%, 4.6% in the brexpiprazole 0.25, 1, 2 mg/day and 4 mg/day short term fixed dose groups and 10.8% in the >4 mg/day short term controlled trials). There were no serious TEAEs related to somnolence and no subject discontinued from IMP due to a TEAE related to somnolence. With the exception of one event of severe sedation, all other TEAEs related to somnolence were mild or moderate in severity. There were no reports of somnolence, hypersomnia, or sedation within the Nervous System Disorders SOC in any treatment group during the Double blind Maintenance phase of trial 331 10 232. A TEAE related to somnolence was reported by 60 subjects (4.2%) in the long-term open-label trial. One subject was discontinued from IMP due to a TEAE related to somnolence. There was 1 serious TEAE related to somnolence. The dose of IMP was not changed and the event resolved.

Prolongation of QT interval is a class effect for atypical antipsychotics. Non-clinical brexpiprazole studies, support an effect of brexpiprazole on QT prolongation. In the Thorough QT Trial 331-10-242, the by gender subgroup analysis showed significant results (upper bound CI > 10 msec) in female subjects both at therapeutic (4 mg) and supratherapeutic (12 mg) brexpiprazole doses (see PK section for details). In Short term controlled trials, within the proposed therapeutic 2-4 mg dose, the incidence of QT prolongation was comparable between brexpiprazole and placebo. Frequencies higher than in PBO were observed only in the brexpiprazole >4 mg group (QTcF ≥ 450 msec 4.4% vs 2.9%; increase in QTcF interval of ≥ 60 msec: 1.1% vs 0.1%) and for the 2-4 g dose only for increase in QTcF interval of ≥ 60 msec: 0.3% vs 0.1%). Available data on frequencies of categorical changes in QT by dose in fixed-dose short-term controlled trials do not show dose dependency in QTcB or QTcF increases in brexpiprazole treated patients between 0.25 and 4 mg dose. In long-term open label trials a new onset QTcF interval over 500 msec and new onset QTcB intervals over 500 msec were each reported in 1 (0.1%) subject (both prolongations were in Subject); a total of 7 subjects (0.5%) had a TEAE related to QT prolongation. There were 8 TEAEs of ECG QT prolonged in 7 subjects. All were considered related to IMP. Two subjects were withdrawn from IMP. An elderly subject with MDD (Subject, treated with brexpiprazole) was discontinued from IMP due to a TEAE of electrocardiogram QT prolonged that was assessed as related to IMP. In long term controlled trial 331-10-232 the incidence of increases of QTcB > 60 msec was 3.2% (3 subjects) in the brexpiprazole group compared with 1.0% (1 subject) in the placebo group. The post-marketing cases of electrocardiogram QT prolonged (3 events retrieved cumulatively cumulatively through 25 Jun 2017 retrieved 3 events, one serious and one leading to withdrawal) each present limited information with confounding histories of cardiac events and concomitant medications, co-suspect medication, or unknown medical and past drug histories. On the basis of the above, QT prolongation has been listed among ADR in section 4.8 of the SmPC. A warning on QT prolongation has been included in section 4.4 of the SmPC providing information on the need to exercise caution when brexpiprazole is prescribed in patients with known cardiovascular disease or family history of QT prolongation, electrolyte imbalance, and in concomitant use with other medicinal products thought to prolong the QT interval, with cross reference to section 4.8 and 5.1 of the SmPC.
The frequency of seizures related TEAEs was similar in short term controlled trial, between the 2-4 mg brexpiprazole dose group and placebo (2 subjects in each group, 0.16% vs 0.27%); a (Patient, from study 14644A) -with no relevant medical history- experienced a serious event, severe in intensity, of grand mal convulsion, leading to withdrawal from the study, 4 days after the first dose of brexpiprazole 4 mg. In long term controlled trial 331-10-232 one event of convulsion was reported in a subject treated with brexpiprazole 4 mg. Two events of seizures (one serious) occurred in long term, open label trials, both leading to withdrawal. Seizures are considered ADRs, based on the observations of seizures both in animal and human studies, and the fact that seizure is a known class effect attributed to antipsychotics.
Blood pressure has been identified as an ADR (in short term controlled trials, TEAEs of blood pressure increased occurred in 0.7% of patients in brexpiprazole 2-4 mg/ day group compared to 0.1% in PBO).
In short-term, controlled Trials, TEAEs related to suicidality were reported by 8 subjects (0.5%, 2 serious events, 1 leading to discontinuation) in the all brexpiprazole treatment group and 3 subjects (0.4%, none serious) in the placebo group. In long-term, Open-label Trials, TEAEs related to suicidality were reported for 23 subjects (1.6%). In Brexpiprazole CDP, one death due to suicide occurred in schizophrenia trials, considered not drug related by the investigator, and 2 deaths due to suicide occurred in MDD trials; one of these case was considered possibly related by the investigator.
Spontaneous cases reporting completed suicide and suicide attempt were reported in the postmarketing setting. In section 4 of the Patient Leaflet, among possible side effects the following is listed “thoughts or feelings about hurting yourself or to commit suicide or a suicide attempt”. Even

though available data do not allow to draw definitive conclusions, the occurrence of cases of suicidal ideation and suicidal attempt should be described also in section 4.8 of the SmPC.
In controlled schizophrenia clinical trials, no deaths occurred in the PBO arm, compared with three deaths (0.1%) in brexpiprazole arms; one found dead 12 days after the end of a 6 weeks brexpiprazole trial, cause of death unknown; for the other two cases of death there were confounding factors/ alternative explanations (12 days after the end of a 6 weeks brexpiprazole trial;). Other 6 deaths occurred in schizophrenia open-label trials, all considered not drug related by the investigators (gastric ulcer perforation/peritonitis:, with no confounding factors, treated with brexpiprazole 2 mg, uterine cancer in a treated with brexpiprazole 4 mg/ day; for the other cases of death -septic shock, cardiac failure, coronary artery disease, completed suicide- there were possible confounding factors). In MDD trials no deaths occurred during the controlled treatment period, while 7 subjects died during the long term open label brexpiprazole trials (2 cases of completed suicide; one case each of: metastatic malignant melanoma, pulmonary embolism, gastric ulcer perforation/peritonitis , ovarian cancer, acute myocardial infarction/ myocardial rupture), all considered not drug related by the investigator, apart from one case of completed suicide considered possibly related; for all the 7 cases of death possible confounding factors were in place.
Other Serious AEs occurred with similar frequencies in short term controlled schizophrenia trials between brexpiprazole (3.4%) and placebo (4.2%). The serious TEAEs reported by more than 1 subject in the brexpiprazole 2 to 4 mg/day group were predominately in the Psychiatric Disorders SOC, including schizophrenia and psychotic disorder.
A higher frequency of ALT (2.2% vs 1%) and AST increased ≥3 x ULN (3% vs 0), of TEAEs associated with hepatic function (3% vs 0), and of discontinuation due to TEAEs related to hepatic function (1% vs 0) occured in brexpiprazole treated subjects compared to PBO in the maintenance phase of long term controlled trial 331-10-232.

3.5. Uncertainties and limitations about unfavourable effects

The only long term controlled safety data come from the 97 brexpiprazole-treated patients within the Double-blind Maintenance phase of Trial 331-10-232 comparing brexpiprazole with placebo (n=105), administered for up to 52 weeks in subjects who were previously stabilized on brexpiprazole 1 to 4 mg/day. Thus in the interpretation of the safety data of this long-term controlled pool it must be taken in consideration that this is a selected patient population (only patients who tolerated brexpiprazole and presented the stability criteria of psychotic symptoms on brexpiprazole 1-4 mg for a consecutive period of 12 weeks were randomized in the maintenance period). Approximately half of the subjects in the brexpiprazole group (52%, n=50) completed 24 weeks of therapy during the Double-blind Maintenance phase compared with 38% of subjects (n=40) in the placebo group. Few subjects (16 brexpiprazole-treated subjects and 9 subjects in placebo group) were treated through Week 52 of the Double-blind Maintenance phase, due primarily to the early termination of the trial. Most patients (63.9%, n=62) received brexpiprazole 4 mg/ day, while 25 patients (25.8%) received brexpiprazole 3 mg/ day.
Other long-term safety data come from Open-label Trials in Schizophrenia, where 1426 patients received brexpiprazole (all doses). 846 subjects (59.3%) were exposed to ≥ 26 weeks of treatment and 654 subjects (45.8%) were exposed to ≥ 52 weeks of treatment. The most frequent modal dose was 4 mg/ day (46%, n= 663), followed by 2 mg/ day (31%, n=442) and 3 mg/ day (20%, n= 279). Other safety data come from the US post marketing setting, as brexpiprazole has been approved for marketing by the US FDA in July 2015, for the following two indications: adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and treatment of schizophrenia. The schizophrenia patient population included in the safety database is not entirely representative of individuals affected by schizophrenia who are the targets of the claimed indication, as elderly subjects,

subjects with psychiatric comorbidities, chronic medical illnesses -including cardiovascular diseases and Insulin-Dependent Diabetes Mellitus- subjects with substance abuse, hepatic impairment and renal impairment have been excluded from clinical trials. Subjects at greatest risk for QT interval prolongation were not included in brexpiprazole clinical trials (exclusion criteria: QTcF ≥ 450 ms, only few included subjects had >65 years of age). Furthermore, common concomitant medications used in schizophrenia were prohibited in the brexpiprazole schizophrenia protocols, thus data regarding brexpiprazole use with concomitant medication in the schizophrenia program is limited.
In light of both non clinical and clinical evidence, the available data do not allow to definitely conclude on the relevance of clinical consequences of hyperprolactinaemia long term.
Studies in animals have shown reproductive toxicity. Brexpiprazole is not recommended during pregnancy and in women of childbearing potential not using contraception.

Only two of the 6 weeks short-term trials included an active controlled arm: Study 14644A, a Phase 3 flexible dose study, included 153 patients treated with quetiapine XR 400-800 mg and Study 331-07-203, a fixed-flexible dose, phase 2 study included 50 patients treated with aripiprazole 15±5 mg. No active comparator is available in long term trials. Compared to the active comparator aripiprazole, 2-4 mg brexpiprazole group presented a higher frequency of PCR weight increase (9.1% vs 4%), PCR prolactin elevations (13.7% vs 0); 4 mg brexpiprazole group presented a higher frequency of extrapyramidal symptoms TEAEs (14.3% vs 12.0%) -mostly driven by a higher frequency of akathisia events (7.1% vs 4.0%) - and of TEAEs of dizziness, syncope or orthostatic hypotension (3.1% vs 2%). The incidence of TEAEs related to somnolence observed with brexpiprazole 2-4 mg was comparable to the one observed with aripiprazole (4.5% vs 4.0%). Compared to the active comparator quetiapine, 2-4 mg brexpiprazole group presented a lower frequency of PCR weight increase (9.1% vs 16.3%), of TEAEs of dizziness, syncope or orthostatic hypotension (2.8% vs 14.4%) and of TEAEs related to somnolence (4.5% vs 26.1%). Conversely, a higher frequency of PCR prolactin elevations was observed with brexpiprazole compared to quetiapine (13.7% vs 8.2%). The highest proposed therapeutic brexpiprazole dose (4 mg) presented a higher frequency of extrapyramidal symptoms TEAEs compared with quetiapine (14.3% vs 9.2%), mostly driven by a higher frequency of akathisia events (7.1% vs 3.9%). However, the limited number of patients included in the groups treated with active comparators should be taken into account in the interpretation of these data.

Only 5 subjects aged ≥65 years were included in short term controlled trials. No subject aged ≥63 years old was enrolled in the long-term, Controlled Trial 331-10-232. In long term open label trials only 30 subjects aged ≥65 years old were enrolled. Elderly patients are expected to have a worse safety profile with antipsychotics. Per clinical trials inclusion criteria, only patients up to 65 years of age were included in clinical trials. Available data do not allow to assess brexpiprazole safety in elderly patients. Elderly patients are expected to have a worse safety profile with antipsychotics.

3.6. Effects Table

Table 47. Effects Table for brexpiprazole for the treatment of adut patients with schizophrenia (data cut-off 31 Dec 2016)

Effect	Short Description	Unit	BREX	PBO	QUE	Uncertainties/ Strength of evidence	References
Improvement in in acute exacerbation of schizophrenia	PANSS Change from baseline at week 6	LSMD vs placebo (95%CI)	2 mg -8.72 (-13.1,-4.37) 4 mg -7.64 (-12.0, -3.30) 2mg -3.08 (-7.23, 1.07) 4mg -6.47 (-10.6, -2.35) 2 mg -7.32 (-13.04, -1.59) 4 mg -3.86 (-9.71, 2.00) 2-4 mg -4.1 (-8.2, 0.1)		400-800mg -8.0 (-12.2, -3.9)	3.6.1.1.1. p< 0.0001 3.6.1.1.2. p= 0.0006 p=0.144 p=0.0022 p=0.0124 p=0.1959 p=0.0002 (QUE) p=0.056 (Brex)	s1
Maintenance of effect/ Relapse prevention	Number of impending relapses (Interim)	N (%)	12 (15.38)	33 (37.08)		p=0.0008, hazard ratio and 95% CI, 0.338 [0.174, 0.655]	s3
	Number of impending relapses (Final)	N (%)	13 (13.54)	48 (38.46)		p<0.001, hazard ratio and 95% CI, 0.292 [0.156, 0.548]	

Unfavourable Effects								
Body weight increase	Incidence of ≥7% increase	%	9.1 2 mg/ day:9.1; 4 mg/ day:8.4	3.8	4	16.3		s1 s2
			5.2	1.0				s3

			20.7				Weight gain increased over time	s4
Hyperglycaemia	Shifts in fasting glucose from normal to high	%	4.5	0			Diabetes Mellitus was an exclusion criteria in BRX CDP	s3
Diabetes mellitus Type 2	TEAEs of type 2 diabetes mellitus	%	0.05 (one SAE)	0				s1
			0.6					s4
Dyslipidemia	TEAEs related to lipids	%	0.7% (8 subjects)	0	0	2%	One event leading to discontinuation	s1
			0.9%					s4
Extrapyramidal Symptoms including akathisia	TEAEs	%	12%	9.6%	12%	9.2%		s1
			2 mg/ day:9.8; 4 mg/ day:14.3	9.9			Dose relationship with higher frequency with higher doses	s2
			6.2%	4.8%				s3
			11%					s4
Akathisia	TEAEs	%	5.9%	4.9%	4.0%	3.9%		s1
			2 mg:5.0%; 4 mg:7.1%	5.6%				s2
			1.03%	0.96%				s3
			5.7					s4

Neuroleptic Malignant Syndrome	TEAEs	n	4					s5
Hyperprolactinaemia	PCR prolactin values (>1 x ULN)	%	F: 13.7% M: 11.1%	6.4% 10.3%	0 0	8.2% 13.4%		s1
			F: 2 mg: 12.1; 4 mg: 15.3 M: 2mg: 11; 4 mg: 15.3	7.3 13.6				s2
			F: 5.3 M: 3.6	2.6 4.9				s3
			F: 19.8 M: 12.9					s4
CPK elevations	>3 x ULN	%	7.7%	5.5%	6.1%	4.2%	Discussion requested on renal function	s1
			1.1%	4.0%				s3
			8.1%					s4
Rhabdomyolysis	TEAEs	N	3	0	1	0	Narratives requested	s1
QT prolongation	QTcB>60 msec	%	3.2%	1.0%			Subjects at greatest risk of QT prolongation excluded from CDP	s3
	TEAEs related to QT prolongation	%	0.5%					s4

Orthostatic hypotension/ dizziness/ syncope	TEAEs	%	2.8%	1.5%	2.0%	14.4%		s1
			2 mg: 2.1% 4 mg: 3.1%	1.4%				s2
			0	3.9%				s3
			2.0%					s4
Somnolence/ Sedation	TEAEs of somnolence, sedation and hypersomnia	%	4.5%	3.8%	4%	26.1%		s1
			2 mg: 3.1% 4 mg: 4.6%				Dose relationship with higher frequency with higher doses	s2
			0	0				s3
			4.2%					s4
Suicidality	TEAEs related to suicidality	%	0.5%	0.4%	0	0		s1
			0	1.9%				s3
			1.6%					s4
Elevation of liver transaminase	ALT increased >=3 x ULN AST increased >=3 x ULN	%	2.2% 3.3%	1.0% 0			One subject met criteria for Hy's Law: to be clarified in which safety pool	s3
	TEAEs related to hepatic function	%	3% (1% leading to discontinuation)	0				s3

Notes:
s1: short term controlled trials: 6 weeks placebo controlled, fixed and flexible dose trials, including also 2 active controlled trials, in schizophrenia patients, under 3 integrated BRX dose groups: <2 mg/day, 2 to 4 mg/day and >4 mg/day)

s2: subgroup of s1: fixed dose (1 mg/ day, 2 mg/ day, 4 mg/ day) short term (6 weeks) placebo controlled phase 3 trials, in schizophrenia patients
s3: double blind maintenance phase of trial 331-10-232 (up to 52 weeks, even though majority of subjects up to 28 weeks, due to early termination) (BRX 1-4 mg/ day)
s4: long term open label trials (up to 52 weeks) (BRX 1-6 mg/ day)
s5: post marketing setting

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Brexpiprazole demonstrated efficacy as measured by reduction at the PANSS scores from baseline to week 6 at the dose of 4 mg (-19.65 points reduction in study 231; -20 points reduction in study 230, -11.49 points reduction in the Japanese study) and at the dose of 2 mg (-20.73 points reduction in study 231; -16.6 points reduction in study 230;-14.95 points reduction in the Japanese study).
Despite results not being replicated for all dose arms in the development program, a reduction of at least 15 points and up to 20 points on average at the PANSS scale is considered clinically relevant.
Despite initial concerns on the MAR imputation used in the MMRM model for the primary statistical analysis, a secondary analysis using a more conservative PMI imputation showed consistent results and a similar magnitude of treatment effect for both primary and secondary endpoints.
In study 14644A the magnitude of treatment effect of quetiapine appeared to be larger than brexpiprazole, and this puts the efficacy of brexpiprazole in context even though it is acknowledged that the trial is not powered for superiority or head to head comparison. Negative results of study 14644A are possibly explained by an unexpectedly high placebo response. The Applicant carried out additional analyses of responders which confirmed that both quetiapine and brexpiprazole differentiated from placebo, in reducing PANSS scores of ≥30% and ≥ 40% but not ≥50% (neither brexpiprazole nor quetiapine achieved 50% PANSS reduction). The change in Personal and Social Performance scale and CGI-I were also statistically significant.
From a safety perspective, brexpiprazole has been investigated comprehensively, however it does not present a clear advantage in terms of adverse event profile. Data from clinical studies clearly indicate that brexpiprazole treatment is associated with weight gain, extrapyramidal symptoms -including akathisia, hyperprolactinaemia, CPK increase, dizziness and sedation.
The Applicant provided a comparison of safety data available for brexpiprazole with data available for other antipsychotics, using both data coming from US product labels and published data. Treatment with brexpiprazole did not present any novel safety findings compared to other atypical antipsychotics indicated for the treatment of schizophrenia. From the available data brexpiprazole compared with aripiprazole appears to have a lower frequency of sedating AEs and insomnia, a similar frequency of akathisia and EPS adverse events and a higher frequency of long term weight gain. A dose-dependency was observed in the frequency of akathisia (3.4%, 5.0%, and 7.1%), Parkinsonism and somnolence, as expected. No robust direct evidence exists to support any safety advantages of this product compared to other similar antipsychotics.

3.7.2. Balance of benefits and risks

In the three fixed-dose placebo-controlled pivotal studies 231, 230, 002 the PANSS score reduction compared to placebo was in the range of 15-20 points and above 20, and therefore it was clinically relevant. The statistical separation from placebo was not confirmed in two dose arms, however this is a common finding in clinical trials for antipsychotics. In study 14644A the magnitude of treatment effect of quetiapine appeared to be larger than brexpiprazole and efficacy of RXULTI was not statistically significant compared to placebo, however the change from baseline in the PANSS score and the

responder analysis confirm a clinically relevant effect also in trial 14644A. Results are consistent across sensitivity analyses.

Like other antipsychotics, brexpiprazole too, has its relatively unique safety profile and no new and unexpected safety signals have been identified with brexpiprazole. Also no robust direct evidence exists to support any safety advantages of this product compared to other similar antipsychotics.

3.8. Conclusions

The overall B/R of RXULTI is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of RXULTI is favourable in the following indication: "RXULTI is indicated for the treatment of schizophrenia in adult patients"

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that brexpiprazole is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.