Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study

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KEY FINDINGS[1]

In this long-term (52 week) randomised, double-blind, placebo-controlled clinical trial of maintenance treatment with REXULTI® (brexpiprazole) vs placebo in adults with schizophrenia:

- Maintained efficacy was demonstrated at a prespecified interim analysis and the trial was terminated early

- Time to impending relapse was statistically significantly delayed with REXULTI vs placebo (p <0.0001); the hazard ratio in the final analysis was 0.292, equating to a 71% reduction in the risk of impending relapse

- A sustained improvement in social functioning was observed with both REXULTI and placebo, though Personal and Social Performance (PSP) score was statistically significantly improved with REXULTI vs placebo, p=0.0071

INTRODUCTION

Prevention of relapse is an important long-term treatment goal after successful treatment of an acute episode of schizophrenia, according to treatment guidelines.[1]

However, many patients do not receive maintenance therapy, despite evidence that it can substantially reduce the risk of relapse. It has been suggested that this may be because patients are not convinced of the need for continued treatment and because antipsychotics can be associated with a substantial side effect burden.[1]

REXULTI (brexpiprazole) is a novel serotonin-dopamine activity modulator approved in Australia for the treatment of adults with schizophrenia.[2] REXULTI acts as a partial agonist at serotonin 5-HT$_{1A}$ and dopamine D$_2$ receptors, and as an antagonist at serotonin 5-HT$_{2A}$ and noradrenaline α$_{1B}$ and α$_{2C}$ receptors, all with similar affinity.[1,2]

This study aimed to complement short-term evidence of efficacy and safety with longer-term evidence by assessing the efficacy, safety and tolerability of maintenance treatment with REXULTI compared with placebo in adults with schizophrenia.[1]

METHODS[1]
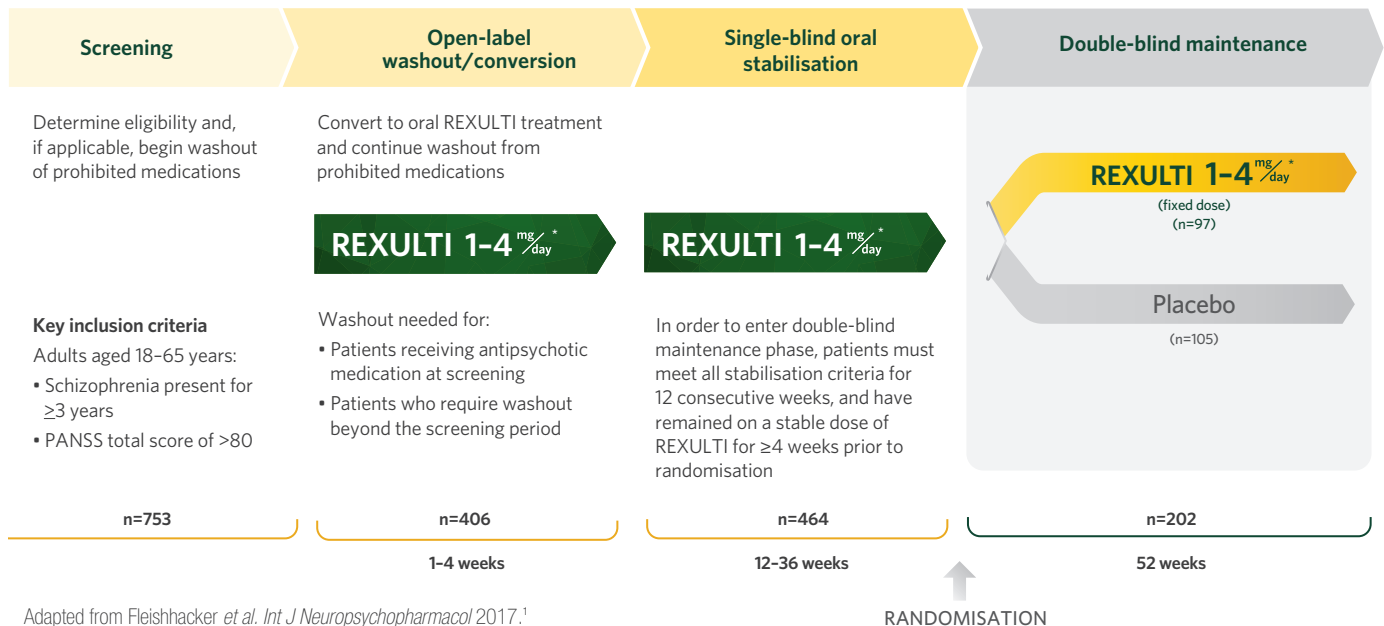
Primary efficacy endpoint

- Primary endpoint: time from randomisation to exacerbation of psychotic symptoms/impending relapse in the double-blind maintenance phase

Secondary efficacy endpoints

- Key secondary endpoint: proportion of patients meeting impending relapse criteria in the double-blind maintenance phase

- Additional secondary endpoints: proportion of patients still meeting stability criteria at their last visit, time to discontinuation for any reason, and mean change in the following scores: PANSS total, positive subscale, and negative subscale scores, CGI-S score, CGI-I score, PSP scale score, GAF scale score, PANSS excited component score, PANSS Marder factor scores and Cogstate computerised cognitive test battery scores.

REXULTI®
brexpiprazole
tablets

Study design[1]

Screening	Open-label washout/conversion	Single-blind oral stabilisation	Double-blind maintenance

Determine eligibility and, if applicable, begin washout of prohibited medications

Convert to oral REXULTI treatment and continue washout from prohibited medications

REXULTI 1–4 $\frac{mg}{day}$ *

REXULTI 1–4 $\frac{mg}{day}$ *

In order to enter double-blind maintenance phase, patients must meet all stabilisation criteria for 12 consecutive weeks, and have remained on a stable dose of REXULTI for ≥4 weeks prior to randomisation

REXULTI 1–4 $\frac{mg}{day}$ *
(fixed dose)
(n=97)

Placebo
(n=105)

Key inclusion criteria
Adults aged 18–65 years:
- Schizophrenia present for ≥3 years
- PANSS total score of >80

Washout needed for:
- Patients receiving antipsychotic medication at screening
- Patients who require washout beyond the screening period

n=753	n=406	n=464	n=202
	1–4 weeks	12–36 weeks	52 weeks

RANDOMISATION

Adapted from Fleishhacker *et al. Int J Neuropsychopharmacol* 2017.[1]

*Recommended maintenance dose is 2–4 mg/day. Refer to approved Product Information for initiation and titration recommendations.[2]

Additional inclusion criteria[1]
- Response to antipsychotic treatment (other than clozapine) in previous year
- Current treatment with oral or depot antipsychotics (other than clozapine) or recent lapse in treament
- History of relapse and/or exacerbation in the absence of antipsychotic treatment

Key exclusion criteria[1]
- DSM-IV-TR® Axis I diagnosis other than schizophrenia
- Acute antidepressant treatment in the previous 30 days
- Antipsychotic-resistant or refractory schizophrenia
- Significant risk of violent behaviour or suicide
- Substance abuse or dependence in the previous 180 days
- Requirement for prohibited concomitant therapy

Antipsychotic conversion[1]
- Cross-titration of patients' current antipsychotic treatment(s) to REXULTI monotherapy occurred over 1 to 4 weeks. REXULTI was initiated at 1 mg/day, and the dose adjusted within the range of 1–4 mg/day over the cross-titration period according to the investigator's judgement

Stabilisation criteria[1]
Stabilisation was defined as meeting all the following criteria for 12 consecutive weeks:
1. Outpatient status
2. PANSS total score of ≤70
3. Lack of specific psychotic symptoms on the PANSS, as measured by a score of ≤4 on each of the following items: conceptual disorganisation, suspiciousness, hallucinatory behaviour and unusual thought content
4. CGI-S score of ≤4 (moderately ill)
5. No current suicidal behaviour as assessed by the C-SSRS
6. No violent or aggressive behaviour resulting in injury or property damage

Preplanned study termination[1]
- Maintained efficacy was demonstrated at a prespecified interim analysis (after 45 events of impending relapse), and the study was terminated early; consequently, a low number of patients completed the maintenance phase (REXULTI, n=14; placebo, n=9)

Dosage[1]
- Mean dose of REXULTI at last visit was 3.4 mg/day in the stabilisation phase and 3.6 mg/day in the maintenance phase

Results[1]

Efficacy

- In the final analysis, time to impending relapse was statistically significantly delayed with REXULTI compared with placebo (p<0.0001); the hazard ratio for the final analysis was 0.292
- In the maintenance phase, the proportion of patients meeting the criteria for impending relapse was 13.5% with REXULTI vs 38.5% with placebo (p <0.0001)
- During the REXULTI stabilisation phase, clinical symptomatology improved as measured on secondary endpoints; the benefits were generally maintained with REXULTI across the 52-week maintenance phase, whereas scores worsened with placebo (LOCF analyses)

Safety

- During the maintenance phase, the incidence of treatment emergent adverse events was comparable to placebo
- Weight changes:
  - Stabilisation phase (REXULTI only): 11.3% of patients experienced a potentially clinically relevant weight gain (≥7% increase). The overall mean weight increase was 0.8 kg
  - Maintenance phase: the incidences of potentially clinically relevant weight gain were 5.2% in the REXULTI group and 1.0% in the placebo group. The overall mean weight decrease from baseline to last visit was –0.3 kg (REXULTI) and –2.2 kg (placebo)
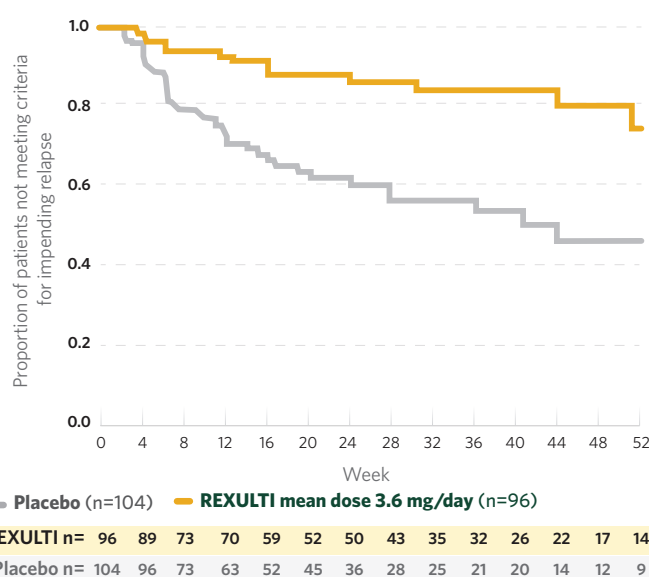
Impending relapse over the 52-week maintenance phase

PRIMARY ENDPOINT

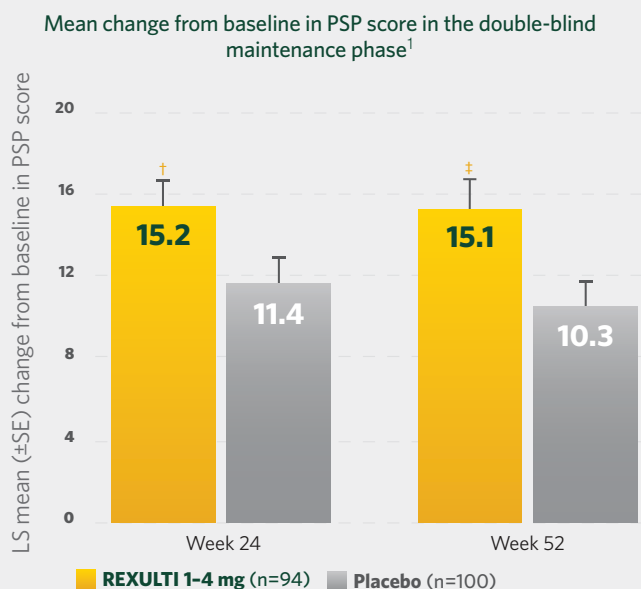| **Time** to impending relapse was statistically significantly increased with REXULTI vs placebo[1] HR= 0.292, p <0.0001 at final analysis[1]	**71%** reduced risk of impending relapse with REXULTI vs placebo[1]

SECONDARY ENDPOINT

REXULTI n=	96	89	73	70	59	52	50	43	35	32	26	22	17	14
Placebo n=	104	96	73	63	52	45	36	28	25	21	20	14	12	9

Placebo (n=104)   REXULTI mean dose 3.6 mg/day (n=96)

Adapted from Fleischhacker *et al. Int J Neuropsychopharmacol* 2017.[1] Maintenance phase efficacy sample, secondary endpoint. Primary endpoint, superiority over placebo on time to impending relapse, was met at the first interim analysis resulting in early termination of the trial, and a low number of patients with week 52 data.[1]

Social functioning as measured on the PSP scale[1]

Mean change from baseline in PSP score in the double-blind maintenance phase[1]

REXULTI 1–4 mg (n=94)   Placebo (n=100)

Adapted from Fleischhacker *et al. Int J Neuropsychopharmacol* 2017 (suppl).[1] LOCF analysis using an ANCOVA model; maintenance phase efficacy sample.
†p<0.05, ‡p<0.01 vs placebo.

The PSP is a clinician-rated scale designed and validated to measure a patient's current level of social functioning.

The PSP consists of 4 items:[3]

Socially useful activities (including work and study)

Self-care

Personal and social relationships

Disturbing and aggressive behaviours

TEAEs that occurred in ≥2% of REXULTI-treated patients and at greater incidence than in placebo-treated patients in the long-term study (randomised double-blind withdrawal phase)[2]

System organ class MedDRA preferred term	REXULTI (n=97) %	Placebo (n=104) %
Gastrointestinal disorders Toothache	3.1	1.0
Metabolism and nutrition disorders Decreased appetite	2.1	0.0
Musculoskeletal and connective tissue disorders Muscle spasms Musculoskeletal pain	2.1 2.1	0.0 1.0
Nervous system disorders Tremor	3.1	0.0
Skin and subcutaneous tissue disorders Pruritus	2.1	0.0

REXULTI is available in four tablet strengths[2§]   BRX 1 mg | BRX 2 mg | BRX 3 mg | BRX 4 mg   Tablets not to actual size

One tablet, once daily[2]   **1**   **Can be taken with or without food**[2]

§The PBS listing of the 1 mg strength of REXULTI does not allow repeats.

ANCOVA = analysis of covariance; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impression-Severity of illness; C-SSRS = Columbia Suicide Severity Rating Scale; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision; GAF = Global Assessment of Functioning; LOCF = last observation carried forward; MedDRA = Medical Dictionary for Regulatory Activities; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance; TEAE = treatment emergent adverse event; TGA = Therapeutic Goods Administration.

PBS Information: Authority required (STREAMLINED).
Code: 4246 for schizophrenia

Please review the REXULTI approved Product Information before prescribing. Product Information is available by calling Lundbeck on 1300 721 277.

Minimum Product Information: Rexulti® (brexpiprazole). **Pharmacology:** Rexulti has pharmacological activity as a serotonin-dopamine activity modulator with antagonistic activity at specific noradrenergic receptors. **Indications:** Treatment of adult patients with schizophrenia. **Contraindications:** Hypersensitivity to brexpiprazole or any of the tablet excipients. **Precautions:** Elderly patients with dementia-related psychosis; suicidality; tardive dyskinesia; neuroleptic malignant syndrome; seizure; cerebrovascular events; hyperglycaemia; diabetes mellitus; orthostatic hypotension; cardiovascular disease, cerebrovascular disease or conditions predisposing to hypotension; venous thromboembolism; body temperature regulation; dysphagia; leucopenia, neutropenia, agranulocytosis; potential impairment of cognitive and motor skills; impulse control disorders; *sleep apnoea**; lactose containing, avoid in patients with galactose intolerance and glucose-galactose malabsorption; concomitant medical illness; pregnancy (Category C); congenital anomalies, neonatal effects; avoid breastfeeding; elderly and children <18 years. **Interactions:** Dosage adjustment is recommended for co-administered strong CYP2D6 or CYP3A4 inhibitors (e.g. quinidine or ketoconazole) strong CYP3A4 inducers (e.g. rifampicin) see Approved PI. **Adverse Effects:** There are no adverse reactions meeting the very common criteria from clinical trials. Common: diarrhoea; dyspepsia, toothache, weight increase, decreased appetite, blood creatinine phosphokinase increase, back pain, pain in extremity, muscle spasm, muscle pain, akathisia, tremor, sedation, pruritus. For further details on all adverse reactions see Approved PI. **Dosage & Administration:** To be taken with or without food. Recommended starting dose is 1 mg once daily on Days 1 – 4. Recommended target dose is 2 mg to 4 mg once daily. Titrate to 2 mg on Day 5 and to 4 mg on Day 8. Consult Approved PI for dosage adjustments for patients with renal or hepatic impairment. **Date of TGA approval:** 17 May 2017; **Date of TGA update:** 24 January 2020; **Date of Minimum PI**: 04 February 2020

*Please note changes to minimum product information in italics

References: 1. Fleischhacker WW *et al. Int J Neuropsychopharmacol* 2017; 20:11–21. 2. REXULTI® Australian Approved Product Information. 3. Morosini PL *et al. Acta Psychiatr Scand* 2000; 101:323–29.

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