PAX-BD Scientific Abstract

DESIGN: Multi-centre, randomised, double-blind, placebo-controlled. Pre-randomisation phase to withdraw antipsychotics and commence mood stabilisers if needed. Remote (on-line and phone) collection of outcome measures to facilitate UK wide recruitment.

SETTING: Secondary care mental health Trusts.

PLANNED INTERVENTIONS: 1:1 allocation to pramipexole (fixed dose to 12 weeks then flexible) or placebo, added to existing mood stabilisers (lithium, valproate, carbamazepine, lamotrigine).

POPULATION: Patients with TRBD (failure of 2 NICE recommended medications). INCLUSION: Bipolar (type I or II); currently depressed (DSM-5 criteria) with consistent QIDS-SR score greater than 10; TRBD; aged over 18; able to provide informed consent. EXCLUSION: DSM-5 severe substance use disorder; current psychotic symptoms; contraindication to pramipexole; history of eye, cardiovascular or renal disease; on antipsychotics at randomisation; currently, planning or at risk of pregnancy; breast feeding; starting specific psychotherapy from 4 weeks before randomisation through to week 12.

OUTCOMES: PRIMARY: QIDS-SR at 12 weeks. SECONDARY: Weekly QIDS-SR and hypomanic symptoms (Altman Self Rating Scale of Mania – ASRM) through to week 52. Anxiety (Genralised Anxiety Disorder 7 – GAD-7), functioning (Work and Social Adjustment Scale – WSAS), quality of life (EQ-5D-5L) & side effect burden (Treatment satisfaction Questionnaire for Medication – TSQM) at weeks 0, 6, 12, 26 and 52. Health economics questionnaire including information on health and social services utilisation, broader societal costs (e.g. lost productivity, informal care) and broader well-being (using the ICECAP-A, OxCAP-MH instruments) collected pre-randomisation, and at 12, 26, 40 and 52 weeks. SAFETY MEASURES: Adverse effects monthly. Suicidality (Columbia–Suicide Severity Rating Scale – CSSRS), impulse control disorders (QUIP-RS), pulse and blood pressure at 1, 6, 12, 26 and 52 weeks. Adherence via pill counts reported by participants and confirmed by Clinical Research Network (CRN) staff.

ANALYSIS: INTERNAL PILOT – quantitative and qualitative data to refine study methodology. MAIN STUDY - Effect of pramipexole on QIDS-SR at 12 weeks compared with placebo using ANCOVA with baseline score among covariates. Clinical & cost-effectiveness over 1 year. Costs, QALYs/capabilities and incremental cost per QALY calculated. No planned interim analyses.

SAMPLE SIZE: 290 participants gives 90% power to detect a 3 point difference in QIDS-SR between drug & placebo at 12 weeks and 80% at 52 weeks, based on the standard deviation (7.0) and dropout rates from CEQUEL study at 12 and 52 weeks (20% and 50% respectively)(1). Three QIDS-SR points equates to Cohen's d=0.4 (considered clinically meaningful). We estimate a 30% drop out during the pre-randomisation period based on the BALANCE study in bipolar disorder, giving a target initial population of 414. All participants followed up to 52 weeks.

RECRUITMENT & TIMETABLE: Recruitment led from 5 academic sites, which link with 40 NHS Trusts, each facilitated by CRN support with additional recruitment from the other local clinical research networks. Internal pilot with stop/go criteria with contingency of expanding recruitment sites. Trial setup 0-6; recruitment 6-30; Internal pilot 6-18; follow up 32-43; analysis/reporting 44-48 months. Official start date (month 0) – April 2018.