F231. GYM RATS: EXERCISE REVERSES COGNITIVE IMPAIRMENT IN THE PHENCYCLIDINE RAT MODEL OF SCHIZOPHRENIA

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Background: The cognitive deficits of schizophrenia have been identified as an unmet clinical need. They are predictive of functional outcome [Green et al., 2000] and quality of life [Fuji et al., 2004], yet there are no treatments able to normalise cognition in schizophrenia. There is increasing evidence that exercise is helpful for these symptoms [Geyer et al., 2012], but the systems involved remain enigmatic. Animal models can be used to scrutinise both the behavioural and biological effects of exercise. The sub-chronic phencyclidine (PCP) rat model for schizophrenia is a well-established and widely utilised model that is used to investigate schizophrenia-like cognitive deficits [Neill et al., 2001]. This two-part study investigates whether voluntary wheel running is able to reverse cognitive impairment in the sub-chronic PCP rat model for schizophrenia, and how long the effect of exercise lasts.

Methods: Female Lister Hooded rats (n=80) were pseudo-randomised into four groups: vehicle-control; vehicle-exercise; PCP-control and PCP-exercise (n=20 per group). Rats were treated either with saline (vehicle) or PCP (2mg/kg, i.p. bi-daily, followed by a seven-day wash-out period). Vehicle and PCP exercise groups had access to a wheel for 1 hour a day, 5 days a week, for 6 weeks. The vehicle and PCP control groups were treated in the same way, but the wheels were locked. Rats were tested in the novel object recognition (NOR) memory paradigm pre-exercise (time point 1, T1) post-exercise (time point 2, T2), after two weeks rest (time point 3, T3) and four weeks rest (time point 4, T4). Half of the animals from each group (n=10 per group) were sacrificed post-exercise (T2), and the remaining animals were sacrificed after 4 weeks rest. For each animal, 1 brain hemisphere was collected for protein analysis and 1 hemisphere was fixed for immunohistochemistry. Behavioural data were analysed using two-way ANOVA and post-hoc t-tests.

Results: Pre-exercise (T1), in the retention phase both vehicle groups were spent more time exploring the novel over the familiar object, an effect that was not seen in the PCP groups. Post-exercise (T2 & T3), in the retention phase both vehicle groups and the PCP exercise group spent more time exploring the novel over the familiar object, an effect that was not seen in the PCP-control group. Post-exercise (T4) in the retention phase both vehicle groups were spent more time exploring the novel over the familiar object, an effect that was not seen in the PCP groups.

Discussion: Exercise is able to rescue the NOR cognitive deficit seen in the sub-chronic rat model for schizophrenia. This corresponds with human studies reporting positive effects of exercise in patients with schizophrenia and provides a potential tool to thoroughly investigate the pro-cognitive effects of exercise. The benefits of the exercise intervention were observed 2 weeks post-exercise with the deficits returning in the PCP treated animals when they were tested 4 weeks post-exercise. Post-mortem analysis is underway to determine the potential mechanisms by which exercise improves cognitive impairment.

F232. A PHASE 3 STUDY TO DETERMINE THE ANTIPSYCHOTIC EFFICACY AND SAFETY OF ALKS 3831 IN ADULT PATIENTS WITH ACUTE EXACERBATION OF SCHIZOPHRENIA

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Background: ALKS 3831, currently under development for the treatment of schizophrenia, is composed of a flexible dose of olanzapine (OLZ) and a fixed dose of 10 mg of samidorphan. In a Phase 2 study, ALKS 3831 mitigated OLZ-associated weight gain and exhibited antipsychotic efficacy similar to OLZ alone. This Phase 3 study assessed antipsychotic efficacy and safety of ALKS 3831 in patients with acute exacerbation of schizophrenia.

Methods: This was an international (USA, Ukraine, Serbia, and Bulgaria), 4-week, randomised, double-blind, active and placebo (PBO)-controlled study of ALKS 3831 in patients with acute exacerbation of schizophrenia (ClinicalTrials.gov: NCT02634346). Eligible patients (N=403) were randomised 1:1:1 to receive either ALKS 3831, OLZ, or PBO. Patients were treated in an inpatient setting for the first 2 weeks of the study and could be treated as inpatients or outpatients for the remaining 2 weeks. Patients were excluded if they received OLZ within 6 months prior to screening. Antipsychotic efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression–Severity (CGI–S), and CGI–Improvement (CGI–I) scales. Safety and tolerability were assessed as adverse events (AEs).

Results: Of 401 patients randomised and dosed to ALKS 3831, OLZ, and PBO, 91%, 89%, and 83% of patients, respectively, completed treatment. The most common reason for discontinuation was withdrawal by patient (6% in both the ALKS 3831 and PBO groups, and 7% in the OLZ group). Baseline characteristics were generally similar between groups; however, baseline mean body-mass index was higher in the OLZ group than in the ALKS 3831 group. Baseline mean ± standard deviation scores were 101.7 ± 11.9 for PANSS total score and 5.1 ± 0.7 for CGI-S score. The mean OLZ dose was 18.4 mg/day in both active treatment arms. Least squares (LS) mean difference ± standard error (SE) versus PBO from baseline to Week 4 in PANSS total score was −6.4 ± 1.8 (P<0.001) for the ALKS 3831 group and −5.3 ± 1.8 (P=0.004) for the OLZ group. LS mean difference ± SE vs PBO from baseline to Week 4 in CGI-S score was −0.38 ± 0.12 (P=0.002) for the ALKS 3831 group and −0.44 ± 0.12 (P<0.001) for the OLZ group. The percentage of patients with an improvement in PANSS response (≥20% improvement from baseline) at Week 4 was 60%, 54%, and 38% in the ALKS 3831, OLZ, and PBO groups, respectively. The percentage of patients with an improvement in CGI-I response (score of ≤2) at Week 4 was 58%, 51%, and 33% in the ALKS 3831, OLZ, and PBO groups, respectively. Discontinuation due to AEs was low in all groups. Common AEs (≥5%) included weight gain, somnolence, dry mouth, anxiety, headache, and schizophrenia.

Discussion: ALKS 3831 demonstrated greater antipsychotic efficacy than PBO, as measured by the PANSS and CGI-S scale, and was similar to the active control, OLZ. The safety profile of ALKS 3831 was similar to OLZ.

F233. NEGATIVE SYMPTOMS ARE INDEPENDENT MODERATOR FACTORS OF TREATMENT RESISTANT SCHIZOPHRENIA EFFECTS ON MULTIPLE CLINICAL, PSYCHOPATHOLOGICAL, COGNITIVE AND PSYCHOSOCIAL VARIABLES

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Background: Negative symptoms (NSs) are more severe in Treatment Resistant Schizophrenia (TRS) than Antipsychotic Responder Schizophrenia (ARS) patients. NSs are predictors of outcomes of neurological soft signs and functional capacity in TRS but not in ARS patients. The scope of this work is to clarify whether NSs effects are integral to or independent from the TRS diagnosis in our sample of patients.

Methods: 70 out of 206 eligible putative TRS and ARS patients were included (enrollment still ongoing). Patients were tested by the Neurological