ARE REPORTS OF MENTAL FOG FROM PATIENTS WITH IDIOPATHIC HYPERSOMNIA MEDIATED BY OBJECTIVE MEASURES OF DAYTIME SLEEPINESS?

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Introduction: Objective evidence of pathological sleepiness (i.e. MSLT < 8) is required for an Idiopathic Hypersomnia (IH) diagnosis. Aside from EDS, IH patients report mental fatigue and inability to concentrate. The relation between these two symptoms is not well understood.

Method: To address this issue we produced a correlation matrix using blinded data from all 21 subjects who, to date, completed the IH202 trial (ARISE[2]). This is a Phase II, double blind, randomized 2-period crossover study in evaluating the safety and efficacy of an oral GABA antagonist (BTD-001). Patients are randomized to either two weeks of active treatment followed by 2-week washout and then two weeks of placebo or placebo followed by washout and then active treatment. Included in the analysis were Idiopathic Hypersomnia Symptom Diary (IHSD) 4 items, the PGIC, SF-36, reports of sleepiness (ESS) and objective measures of sleepiness (MWT and PVT). We produced 2 correlational matrices (Pearson Correlation Coefficients) using data from the 21 subjects who completed both treatment periods in the ARISE[2] study. We produced this matrix using blinded pooled data from treatment period 1 as well as treatment period 2. Importantly, approximately half the subjects in treatment period 1 were on drug and the other half were on placebo. In treatment period 2, those previously on placebo were on active treatment and those previously getting active were on placebo. The advantage of this approach is the ability to identify correlates of patient's evaluation of improvement in a double-blind manner. As there were multiple correlations performed, we treated treatment periods 1 and 2 correlations as replicates and are considering only those that were significant in both matrices.

Results: There were 55 correlations calculated in each treatment period. Across 55 correlations, 24 were not significant in either treatment periods, 19 were significant at one of the treatment periods, and 12 were significant in both treatment periods. Patient evaluation of improvement (i.e. PGIC) correlated on both occasions with only Mental Fog and Exhausted scales Scale of the IHSD and the vitality sub-scale of the SF-36. Neither measure of the 2 objective assays of sleepiness (MWT and PVT) correlated even once with subject's estimate of improvement. Interestingly, neither of the 2 objective assays of sleepiness correlated even once with the patient report of sleepiness (i.e. ESS). This suggests, as authors have stated previously that the reports of sleepiness in IH relate more to mental fatigue rather than physiological sleepiness per se. In contrast the mental fog scale, correlated with all 3 of the other IHSD subscales, the subjective sleepiness (ESS) as well as patients´ judgments about efficacy (PGIC).

Discussions: These data support the positions that: a) mental fog is independent of objective assays of sleepiness and b) objective assays of sleepiness may not be appropriate efficacy endpoints in IH clinical trials.