Biomarker Profiling of NSI-189 Phosphate, a Neurogenic Compound, in Patients with Major Depressive Disorder (MDD) during a Phase Ib Randomized Double-Blind, Placebo-Controlled Trial

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Background

NSI-189 Phosphate, (4-benzylpiperazin-1-yl)[2-(3-methyl-butyramino)pyridin-3-yl] methane is a novel molecule developed by Neuralstem, Inc. for the treatment of MDD, based upon preclinical data demonstrating stimulation of neurogenesis of human hippocampus-derived neural stem cells in vitro and in mouse hippocampus in vivo.

In a Phase Ib, double-blind, placebo-controlled, multiple-ascending-dose study, patients with symptomatic MDD were randomized to receive NSI-189 40, 80, or 120 mg daily or placebo for 28 days.

Aim: Few biomarkers of antidepressant treatment response are in current use as an adjunct to clinical response measurements made using subjective clinical assessment tools. Our aim was to explore biomarkers in the MDDScoreTM test panel for the ability to monitor efficacy during a trial of NSI-189.

Study Design

This was a Phase Ib, double-blind, randomized, placebo-controlled, multiple-dose study with 3 ascending cohorts. Twenty-four patients with MDD were recruited, with their diagnosis and illness severity confirmed through an independent, remote SAFER interview from the MGH CTNI raters.

Each cohort included at least 3 female subjects. Each patient underwent a screening for eligibility (Day -37 to Day -6 or -3), and eligible patients were admitted into the unit on Day -5 to complete antidepressant washout and undergo baseline assessments. Patients were randomized (3:1) to receive NSI-189 phosphate or placebo for 28 days. Cohort 1 received NSI-189 (or placebo) 40 mg QD; Cohort 2, NSI-189 (or placebo) 40 mg BID; Cohort 3, NSI-189 (or placebo) 40 mg TID.

During the 28-day, multiple-dose period, patients underwent traditional safety and pharmacokinetic assessments.

Methods

During dosing and follow up, patients underwent traditional safety and pharmacokinetic assessments. Assessments included the CFFQ, CGI-S, C-SSRS, MADRS, and the SDQ. Plasma samples were tested by immunoassay for plasma levels of 10 biomarkers (A1AT, ApoC3, BDNF, Cortisol, EGF, MPO, Prolactin, Resistin, sTNFR2 and TSH) at 2 week intervals.

In our regression analysis, we used a reduction of greater or equal to 15.9 units in MADRS scores at Day 28 (end of treatment) as indicative of rapid clinical response to NSI-189 (Table 2).

Assessments

Patient Population

Each subject had a blood sample drawn at the indicated time points ranging from -5 to 84 days. Plasma was stored frozen at -70°C until shipment to Ridge for measurement of ten plasma biomarkers (Alpha-1 Antitrypsin, Apolipoprotein C3, Brain Derived Neurotrophic Factor, Cortisol, Epidermal Growth Factor, Myeloperoxidase, Prolactin, Resistin, Soluble TNF Receptor II and Thyroid Stimulating Hormone) by immunoassay.

Table 1. Number of NSI-189 treated patients and percent classified into MADRS PR and RM groups

Results

A significant number of NSI-189 treated patients demonstrated clinical improvement by a reduction in total MADRS scores ≥15.9 points which was sustained beyond the active dosing period. At 8 weeks, this sustained drop was to a point at or near what is usually associated with SSRI remission (Thase et al. The British Journal of Psychiatry 199: 501-507, 2011). Analysis of the data on the plasma level of each individual biomarker at baseline (Day 1; Table 1) indicated that there were no significant differences between patients treated with NSI-189 or placebo prior to treatment. We developed a linear regression-based model utilizing baseline plasma levels of BDNF, EGF, MPO, sTNFR2 and A1AT which was able to identify a rapid response to NSI-189, consistent with therapeutic effects shown by the traditional clinical measures.

Summary and Conclusions

NSI-189 is rapidly and persistently efficacious. Preliminary analysis of this small sample set suggests that prediction of response to NSI-189 may be possible from baseline biomarker profiling.

Disclosures: Drs. Bilello and Thurmond are employees and stockholders of Ridge Diagnostics, Inc. Ms. Feng was a statistician employed by Ridge. Dr. Lev Gertsik was the PI of the study at CTT and is Medical Director at PAREXEL, Los Angeles. Drs. English and Ereshefsky are Senior Director and VP Early Phase CNS, respectively at PAREXEL. Drs. Fava, Hoeppner, Mischoulon, Kinrys, and Freeman are associated with Harvard, MGH and the CTNI. Ms Flynn is Director of Clinical Trial Operations, MGH CTNI. Dr. Johe co-founded Neuralstem, Inc. and is its Chief Scientific Officer.