CHS-131, an Oral, Once-Daily Selective Modulator of PPARγ Inhibited Contrast Enhancing Lesions and Reduced Cortical Atrophy Over a 6-month Phase 2B Study in RRMS

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Background: CHS-131 is a novel, first-in-class, selective modulator of PPARγ that crosses the blood-brain barrier and is thought to exert potent anti-inflammatory effects in the central nervous system without evidence of systemic immunosuppression. CHS-131 has been studied in over 600 patients in multiple indications and has been shown to improve clinical and neuropathological outcomes in animal models of experimental autoimmune encephalomyelitis. This study was designed to evaluate safety and efficacy of CHS-131 in treatment-naïve subjects with relapsing remitting multiple sclerosis (RRMS).

Methods: This double-blind, parallel-group, 2 part study randomized patients into one of three arms: oral CHS-131 at 3 mg; oral CHS-131 at 1 mg; or oral placebo in a 1:1:1 ratio at 21 sites in Russia. Patients (age 18-50 years) had RRMS for ≤3 years, ≥1 gadolinium-positive lesion within 12 months of enrollment, an Expanded Disability Status Score (EDSS) of 0-6 at screening. In Part 1, the primary endpoint was the cumulative number of new gadolinium contrast enhancing (CE) T1-weighted lesions seen on monthly magnetic resonance imaging (MRI) over 6-months. All MRIs were read in a blinded fashion at a U.S. imaging center. Part 2 is an open label, 6-month, safety extension study, in which all subjects transition to 1 mg CHS-131 daily, to evaluate clinical response, CE lesions, and safety (not reported here).

Results

227 subjects with RRMS were enrolled (mean age 31 years; 65% female; 97% completed Part 1). Treatment with CHS-131 resulted in a reduction of CE lesions: the mean cumulative number of new CE lesions over 6 months was 4.2 (LSMean 3.10) for 3 mg CHS131 (n=70), 7.6 (LSMean 5.15) for 1 mg CHS131 (n=70), and 7.8 (LSMean 6.49) for placebo (n=69). The response was dose-dependent, and based on statistical modeling, the incidence of new CE lesions with 3 mg CHS-131 was significantly lower (52% reduction) than with placebo (p=0.003), and the incidence with 1 mg CHS-131 was 21% lower than with placebo (p=ns). In addition, the treatment with 3 mg of CHS-131 reduced the loss of cortical volume by 42.6% at 3 months and 34.2% at 6 months, as compared to placebo. The extent of cortical atrophy was similar between placebo and 1mg/d CHS-131.

Treatment Emergent Adverse Events (AE) were reported in 32.9%, 26.3%, and 36.0% of patients in the 3 mg CHS-131, 1 mg CHS-131, and placebo groups, respectively, and 10.5%, 3.9%, and 6.7% of subjects had AEs judged to be related to treatment. No new safety signals were detected for CHS-131. There was no evidence of immunosuppression or toxicities (e.g., edema, weight gain) common to full PPARγ agonists.

Conclusions

This study demonstrated both a statistically significant decrease in cumulative incidence of CE lesions, and moderation of the progression of neural atrophy with 3 mg CHS-131 in comparison with placebo at 6-months of treatment. CHS131 was well tolerated. Further study is warranted.