Introduction

- Trodusquemine is the first drug candidate that acts both centrally and peripherally to selectively inhibit protein tyrosine phosphatase 1B (PTP1B). By inhibiting PTP1B, trodusquemine is expected to decrease appetite and normalize blood sugar as PTP1B is central to both insulin and leptin signaling pathways.

- Weight loss effects have been previously reported in models of obesity and genetically obese rodents treated with Trodusquemine.1,4

- Trodusquemine is currently under evaluation for the treatment of obesity and comorbidities such as type 2 diabetes.

Objectives

- To evaluate the safety and tolerance of single ascending intravenous doses of trodusquemine in a special population.
- To further evaluate the pharmacokinetics of trodusquemine.
- To assess whether trodusquemine has an effect on appetite, psychomotor function, mood, and selective biomarkers.

Methods

This study was conducted in overweight or obese male and female subjects with type 2 diabetes mellitus and was a double-blind, randomized, placebo-controlled design. Each subject received a single intravenous dose of trodusquemine or placebo via a 2-hour infusion and remained in the study center for a minimum of 12 hours. Trodusquemine was administered in doses of either 0.6, 1.5, or 5.0 mg/m² in each dose group. Subjects received trodusquemine and 2 subjects received placebo (vehicle control). Potential effects of trodusquemine on psychomotor function or mood state were evaluated by using the Brief Psychiatric Rating Scale (BPRS) and the Montgomery-Asberg Depression Rating Scale (MADRS).

The safety and tolerability of trodusquemine in subjects with type 2 diabetes using a double-blind, randomized, placebo-controlled design. Each subject received a single intravenous dose of trodusquemine in a special population. The majority of these TEAEs were judged to be treatment-emergent adverse events (TEAEs). There were no severe adverse events, or serious adverse events (SAEs) reported in the study.

Results

The study was conducted at two research sites. Twenty-eight subjects (18 placebo and 10 trodusquemine) were enrolled and received study medication. There were 17 female and 11 male subjects enrolled. The average age of subjects receiving active drug was 51.7 years, while that of subjects receiving placebo was 49.6 years.

Conclusions

MSI-1436, a centrally acting inhibitor of PTP1B, was well-tolerated in a study of a diabetics type 2 diabetes. The safety profile supports further study of MSI-1436 in obese and metabolically challenged patients.

PBO 3mg/m2 6mg/m2 10mg/m2 15mg/m2

\% Weight loss Day -1 to 3

MSI-1436C-103 Adverse Events Summary

Overall, approximately % of all subjects receiving trodusquemine and % of subjects receiving placebo reported at least 1 Treatment Emergent Adverse Event (TEAE). The majority of these TEAEs were judged to be mild in severity and considered unrelated to study drug administration. There were no severe adverse events, or serious adverse events (SAEs) reported in the study.

No clinically significant changes were noted in vital signs or physical examinations. There was no meaningful impact on cardiac conduction on 12-lead ECGs. There were no ECG abnormalities considered to be clinically significant by the Investigators, and no cardiovascular AEs were reported during the study.

Conclusions

Based on a preliminary review of MSI-1436C-103 data we conclude:
- Subjects in study MSI-1436C-103 experienced a minimal number of adverse events, with few related events and no serious adverse events.
- There were no clinically meaningful changes in any clinical safety laboratory or specialized biomarker.
- The pharmacokinetic parameter estimates from studies MSI-1436C-102 and MSI-1436C-101 are comparable.

Evaluating Cmax and AUC across both studies, drug exposure increased in a manner consistent with dose proportionality.

Based on data from these two studies, selection of every third day dosing in the proposed ascending multiple dose study, MSI-1436C-102, is appropriate.

References