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ABSTRACT: Background: The Genomics Used to Improve DEpresssion Decisions (GUIDED) trial assessed outcomes associated with combinatorial pharmacogenomic (PGx) testing in patients with major depressive disorder (MDD). Analyses used the 17-item Hamilton Depression (HAM-D17) rating scale; however, studies demonstrate that the abbreviated, core depression symptom-focused, HAM-D6 rating scale may have greater sensitivity toward detecting differences between treatment and placebo. However, the sensitivity of HAM-D6 has not been tested for two active treatment arms. Here, we evaluated the sensitivity of the HAM-D6 scale, relative to the HAM-D17 scale, when assessing outcomes for actively treated patients in the GUIDED trial.

METHODS: Outpatients (N=1,298) diagnosed with MDD and an inadequate treatment response to >1 psychotropic medication were randomized into treatment as usual (TAU) or combinatorial PGx-guided (guided-care) arms. Combinatorial PGx testing was performed on all patients, though test reports were only available to the guided-care arm. All patients and raters were blinded to study arm until after week 8. Medications on the combinatorial PGx test report were categorized based on the level of predicted gene-drug interactions: 'use as directed', 'moderate gene-drug interactions', or 'significant gene-drug interactions.' Patient outcomes were assessed by arm at week 8 using HAM-D6 and HAM-D17 rating scales, including symptom improvement (percent change in scale), response (≥50% decrease in scale), and remission (HAM-D6 ≤4 and HAM-D17 ≤7).

RESULTS: At week 8, the guided-care arm demonstrated statistically significant symptom improvement over TAU using HAM-D6 scale (Δ=4.4%, p=0.023), but not using the HAM-D17 scale (Δ=3.2%, p=0.069). The response rate increased significantly for guided-care compared with TAU using both HAM-D6 (Δ=7.0%, p=0.004) and HAM-D17 (Δ=6.3%, p=0.007). Remission rates were also significantly greater for guided-care versus TAU using both scales (HAM-D6 Δ=4.6%, p=0.031; HAM-D17 Δ=5.5%, p=0.005). Patients taking medication(s) predicted to have gene-drug interactions at baseline showed further increased benefit over TAU at week 8 using HAM-D6 for symptom improvement (Δ=7.3%, p=0.004) response (Δ=10.0%, p=0.001) and remission (Δ=7.9%, p=0.005). Comparatively, the magnitude of the differences in outcomes between arms at week 8 was lower using HAM-D17 (symptom improvement Δ=5.0%, p=0.029; response Δ=8.0%, p=0.008; remission Δ=7.5%, p=0.003).

CONCLUSIONS: Combinatorial PGx-guided care achieved significantly better patient outcomes compared with TAU when assessed using the HAM-D6 scale. These findings suggest that the HAM-D6 scale is better suited than is the HAM-D17 for evaluating change in randomized, controlled trials comparing active treatment arms.
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Confirmed Safety of Deutet.rabenazine for Tardive Dyskinesia in a 3-Year Open-Label Extension Study

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ABSTRACT: Background: Deutetrabenazine (Austedo) is approved by the FDA for treatment of tardive dyskinesia

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(TD) in adults. In the 12-week ARM-TD and AIM-TD studies, deutetrabenazine showed clinically significant improvements in Abnormal Involuntary Movement Scale (AIMS) scores compared with placebo, and there were low rates of overall adverse events (AEs) and discontinuations associated with deutetrabenazine. The objective of this study was to evaluate the long-term safety and tolerability of deutetrabenazine in patients with TD at 3 years.

METHODS: Patients who completed ARM-TD or AIM-TD were included in this open-label, single-arm extension study, in which all patients restarted/started deutetrabenazine 12 mg/day, titrating up to a maximum total daily dose of 48 mg/day based on dyskinesia control and tolerability. The study comprised a 6-week titration period and a long-term maintenance phase. Safety measures included incidence of AEs, serious AEs (SAEs), and AEs leading to withdrawal, dose reduction, or dose suspension. Exposure-adjusted incidence rates (EAIRs; incidence/patient-years) were used for calculating AE frequencies. This analysis reports results up to Week 158.

RESULTS: A total of 343 patients were enrolled (111 received placebo and 232 received deutetrabenazine in the parent studies). At the time of this analysis, 183 patients were still receiving treatment; 259 completed 1 year, 172 completed 2 years, and 41 completed 3 years. There were 623 patient-years of exposure. More than 40% of patients reached the maximum dose. EAIRs of AEs were comparable to or lower than those observed in the ARM-TD and AIM-TD short-term randomized trials of deutetrabenazine vs. placebo. The frequency of SAEs (EAIR 0.10) was similar to that observed with short-term placebo (0.33) and short-term deutetrabenazine (range 0.06–0.33) treatment. AEs leading to withdrawal (0.06), dose reduction (0.10), and dose suspension (0.05) were uncommon.

CONCLUSION: These results support the safety outcomes observed in the ARM-TD and AIM-TD parent studies and the safety of deutetrabenazine for long-term use in patients with TD.

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Development of Deutetrabenazine as a Potential New Non-Antipsychotic Treatment for Tourette Syndrome in Children and Adolescents

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ABSTRACT: Background: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by the hyperkinetic movements of motor and phonic tics manifested in young age. Currently approved treatments in the United States are antipsychotics: haloperidol, pimozide, and aripiprazole, which are associated with serious side effects, including tardive dyskinesia (TD). Deutetrabenazine, a vesicular monoamine transporter type 2 (VMAT2) inhibitor, was approved in 2017 by the US FDA for the treatment of chorea associated with Huntington's disease and TD. Three ongoing studies (Alternatives for Reducing Tics in TS [ARTISTS]) are evaluating the efficacy, safety, and tolerability of deutetrabenazine in reducing tics in TS in children and adolescents (age 6-16 years).

METHODS: ARTISTS 1, a phase 2/3, response-driven, dose-titration, placebo-controlled study, randomizes patients (N=116) 1:1 to deutetrabenazine or placebo for 12 weeks. ARTISTS 2, a phase 3, fixed-dose study, randomizes patients (N=150) 1:1:1 to deutetrabenazine high or low dose, or placebo for 8 weeks. The primary efficacy outcome in these pivotal studies is change from baseline to end of treatment in the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS). Additional efficacy endpoints and safety/tolerability are also evaluated. ARTISTS is a 56-week, open-label, single-arm, long-term safety/tolerability study in patients who have successfully completed either ARTISTS 1 or ARTISTS 2.

RESULTS: Not available yet.

CONCLUSION: TS can have potentially long-term life impact, and there remains unmet medical need for effective and well-tolerated treatments. Three ARTISTS studies will evaluate the efficacy, safety, and tolerability of deutetrabenazine in patients with tics in TS.

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