Mavoglurant in adolescent patients with Fragile X Syndrome: Results of a randomized, double-blind study

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Background

Mavoglurant (AFQ056), a selective metabotropic glutamate receptor 5 antagonist, has been evaluated for the treatment of behavioral symptoms of Fragile X Syndrome (FXS). Here, the efficacy and safety of mavoglurant in adolescent patients (12-17 years) with FXS are reported.

Methods

This was a phase II, multicenter, randomized, double-blind (DB), placebo-controlled, parallel-group study (NCT01357239). After a 4-week, single-blind, placebo run-in period, patients were randomized to mavoglurant (25, 50, or 100 mg BID) or placebo (1:1:1:1). After a protocol amendment, patients were randomized (1:1) only to mavoglurant 100 mg BID and placebo groups. In the DB phase, patients were initiated on 25 mg BID and were up-titrated to the target dose. The key endpoints were change from baseline to Week 12 in behavioral symptoms based on the Aberrant Behavior Checklist—Community edition using the FXS specific algorithm (ABC-C_{FX}) total score in patients with completely methylated (CM) (primary endpoint: after treatment with mavoglurant 100 mg BID) and partially methylated (PM) Fragile X Mental Retardation 1 (FMR1) gene, individual subscales of ABC-C_{FX}, and rating of change on Clinical Global Impression—Improvement (CGI-I). Safety assessments included adverse events (AEs), serious AEs, ECGs and laboratory evaluations.

Results

Of 139 randomized patients, 135 completed the study. Two of the 4 non-completers discontinued due to AEs. In the CM stratum, reduction in the ABC-C_{FX} total score vs, placebo (-9.4) over 12 weeks was not statistically significant for mavoglurant 25 mg BID (-11.8) and 50 mg BID (-3.4) groups, but was significant for the 100 mg BID (8.6) group following multiplicity adjustment in favor of placebo. In the PM stratum, there was no significant difference in any of the mavoglurant groups (25 mg BID: -6.8; 50 mg BID: -2.8; 100 mg BID: -5.7) vs placebo (-3.5), following multiplicity adjustment. Changes in ABC-C_{FX} subscale and CGI-I scores for the mavoglurant groups did not demonstrate benefits compared with placebo. The majority of AEs were mild with no clinically relevant changes in ECGs or laboratory assessments.

Conclusion

Treatment with mavoglurant over 12 weeks did not demonstrate benefits compared with placebo for multiple behavioral symptoms on various efficacy scales. There was no evidence for an impact of methylation of FMR1 gene on response to mavoglurant on any of the efficacy measures assessed. Overall, mavoglurant was well tolerated.

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