# Mavoglurant in fragile X syndrome: Results from two phase II randomized, double-blind trials

Apostol G[1], Berry-Kravis E[2], Hagerman RJ[3], des Portes V[4], von Raison F[1]

[1]Neuroscience Development, Novartis Pharma AG, Basel, Switzerland
[2]Departments of Pediatrics, Neurological Sciences, and Biochemistry, Rush University Medical Center, Chicago, IL
[3]Medical Investigations of Neurodevelopmental Disorders, Institute University of California, Davis, Sacramento, CA
[4]National Reference Center for Fragile X and Other XLMR, Hospices Civils de Lyon, Université de Lyon and CNRS UMR 5230 (L2C2), Bron, France

## 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 results of mavoglurant in adolescent (12-17 years) (NCT01357239) and adult (18-45 years) (NCT01253629) patients with FXS are reported.

## Methods

These were phase II, multicenter, randomized, double-blind (DB), placebo-controlled, parallel-group studies. 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). In the adolescent study, after a protocol amendment, patients were randomized (1:1) only to the mavoglurant 100 mg BID or placebo. In the DB phase, patients initiated with 25 mg and were up-titrated to the target dose. The key endpoints were change from baseline to Week 12 in Aberrant Behavior Checklist—Community edition using the FXS specific algorithm (ABC-$C_{FX}$) total score in patients with completely methylated (CM) Fragile X Mental Retardation 1 (FMR1) gene and partially methylated (PM) 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

A total of 135 of 139 randomized patients completed the adolescent study and 162 of 175 randomized patients completed the adult study. In both the CM and PM strata in both studies, no statistical significance was reached in favor of mavoglurant at any of the dose for reduction in ABC-$C_{FX}$ total score vs. placebo over 12 weeks. Treatment with mavoglurant did not demonstrate benefits vs placebo for multiple behavioral symptoms as measured by ABC-$C_{FX}$ subscale scores and CGI-I in both the studies. The majority of AEs were mild in severity. There were no clinically relevant changes in ECGs or laboratory tests.

## Conclusion

Treatment with mavoglurant over 12 weeks did not demonstrate benefits vs 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.


## Funding statement

These studies are funded by Novartis Pharma AG.

Berry-Kravis E has received funding from Seaside Therapeutics, Novartis, Roche, and Neuren to conduct clinical trials in FXS; from Novartis and Roche to consult on trial design; from Asuragen Inc to develop testing standards for FMR1 testing; and from SynapDx to develop testing to predict risk of autism. des Portes V is an employee of the Centre Université de Lyon, France. His institution has received compensation from Novartis Pharma AG for the clinical investigation of new drugs, and he is currently involved in ongoing clinical trials with Novartis Pharma AG. Hagerman RJ is an employee of Institute University of California, Davis, Sacramento, CA, and has received funding from Novartis, Roche, Seaside Therapeutics, Forest, Neuropharm, Curemark, and Johnson and Johnson for clinical trials. Apostol G and von Raison F are employees of Novartis and hence may be eligible for Novartis stock and stock options.