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MONOGRAPH

# MAVOGLURANT

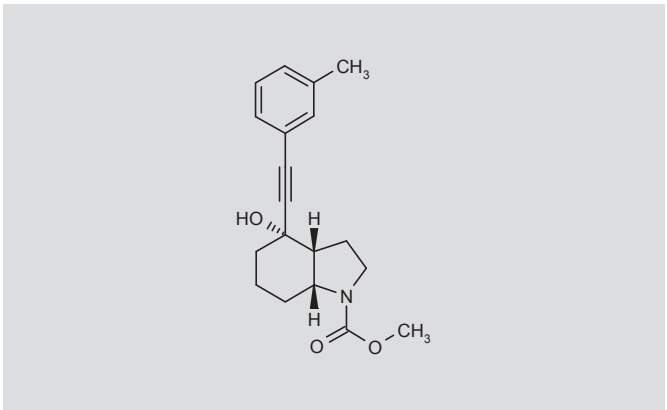
Rec INN

*Metabotropic Glutamate $mGlu_5$ Receptor Antagonist*
*Treatment of Fragile X Syndrome*
*Treatment of Dyskinesia*

AFQ-056
GW-579769
Rezonic™
Zunrisa™

(–)-(3a*R*,4*S*,7a*R*)-4-Hydroxy-4-[2-(3-methylphenyl)ethynyl]perhydroindole-1-carboxylic acid methyl ester

InChI: 1S/C19H23NO3/c1-14-5-3-6-15(13-14)8-11-19(22)10-4-7-17-16(19)9-12-20(17)18(21)23-2/h3,5-6,13,16-17,22H,4,7,9-10,12H2,1-2H3/t16-,17-,19-/m1/s1




$C_{19}H_{23}NO_3$
Mol wt: 313.3908
EN: 342768

**SUMMARY**

*The role of glutamate as the major excitatory neurotransmitter in the brain, the wide distribution of glutamate receptors in the central nervous system and their role in regulating cell excitability and synaptic transmission mean that drugs targeting glutamate transmission may have activity relevant to a large number of neurological and psychological disorders. Research into the metabotropic glutamate receptor (mGlu) has led to multiple therapeutic possibilities. A wide range of experimental and biological evidence implicates the group I $mGlu_5$ receptor in two otherwise disparate conditions: fragile X syndrome (FXS) and levodopa-induced dyskinesia (LID). $mGlu_5$ receptor antagonists are being investigated for these indications, and the $mGlu_5$ receptor antagonist mavoglurant has reached phase II/III development for FXS and phase II development for LID. Mavoglurant has been found to be a potent and selective $mGlu_5$ receptor antagonist. The agent showed promise in mice lacking the gene responsible for development of FXS (Fmr1) in a test of hypersensitivity and reduced dyskinesias in the MPTP-lesioned monkey model of Parkinson's disease. Mavoglurant had beneficial effects in a clinical trial in individuals with FXS, with effects dependent on FMR1 promoter methylation status. Mavoglurant was also associated with significant antidyskinetic effects in two phase II trials. Several clinical studies of mavoglurant in FXS and LID are planned or currently under way.*

**Key words:** Metabotropic glutamate receptor – Fragile X syndrome – Dyskinesia – Mavoglurant – AFQ-056 – GW-579769

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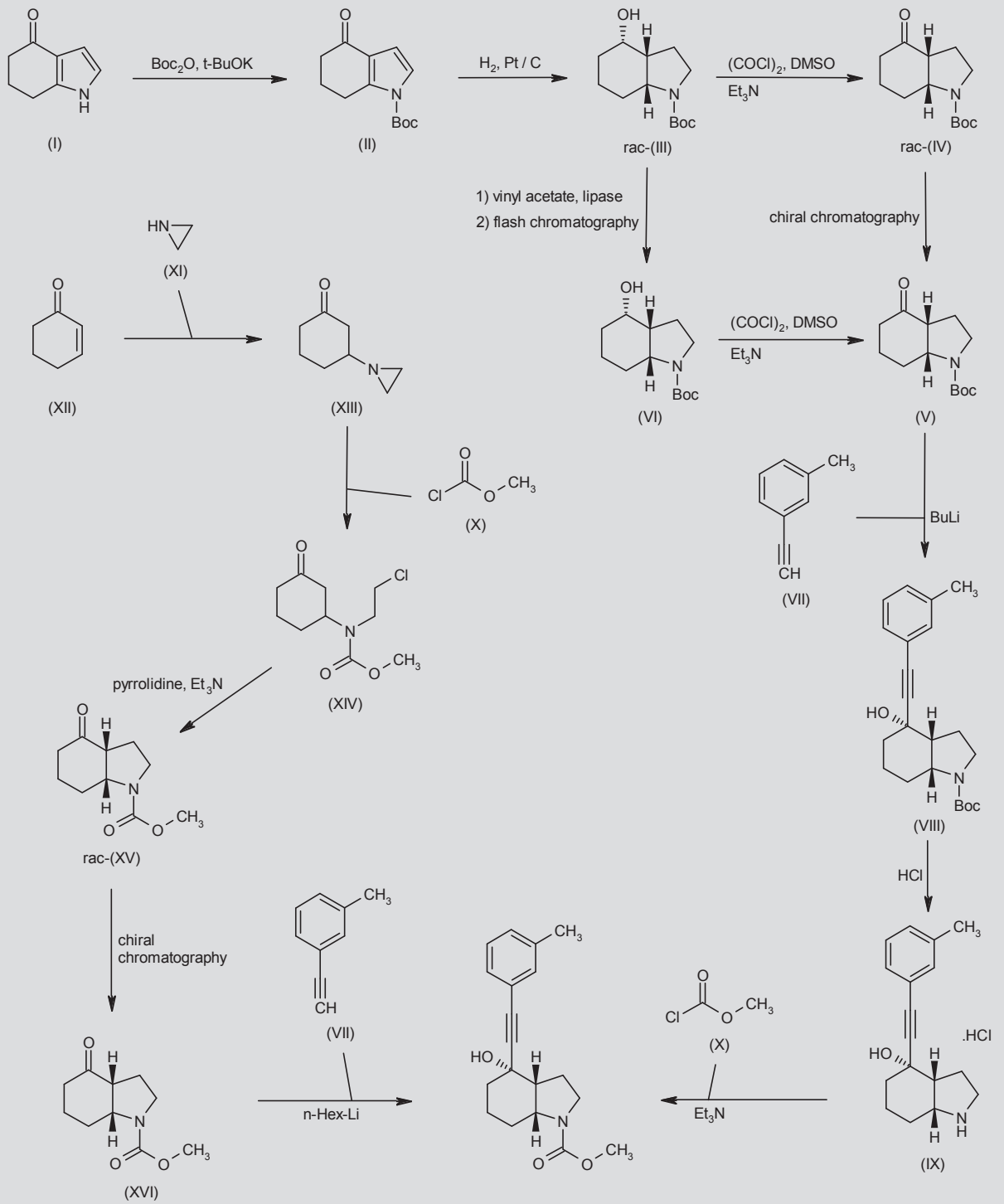
**SYNTHESIS***

Protection of 1,5,6,7-tetrahydroindol-4-one (I) with $Boc_2O$ by means of *t*-BuOK in refluxing THF gives the corresponding *N*-Boc-indolone (II), which is then reduced with $H_2$ over Pt/C in MeOH to yield (3a*R**, 4*S**,7a*R**)-*cis*-*N*-Boc-4-hydroxyoctahydroindole (III). Swern oxidation of alcohol (III) using $(COCl)_2$, DMSO and $Et_3N$ in THF affords the racemic perhydroindolone (IV), which is resolved using chiral chromatography to the (3a*R*,7a*R*)-enantiomer (V). Alternatively, enantioselective acetylation of racemic alcohol (III) with vinyl acetate in the presence of immobilized *Candida antarctica* lipase (Novozyme 435), followed by flash chromatographic separation of the undesired (3a*S*,4*R*,7a*S*)-acetate provides unreacted (3a*R*,4*S*,7a*R*)-alcohol (VI), which is then oxidized to ketone (V) under Swern conditions. Treatment of 1-ethynyl-3-methylbenzene (VII) with BuLi in THF at –20 °C and subsequent enantioselective condensation with ketone (V) leads to propargylic alcohol (VIII), which is then *N*-deprotected with HCl in EtOAc to produce the amine (IX). Finally, amine (IX) is acylated with methyl chloroformate (X) in the presence of $Et_3N$ in $CH_2Cl_2$ (1). Scheme 1.

Alternatively, Michael addition of aziridine (XI) to 2-cyclohexenone (XII) in toluene gives 3-(1-aziridinyl)cyclohexanone (XIII), which is submitted to aziridine ring opening by treatment with methyl chloroformate in toluene to provide methyl *N*-2-chloroethyl-*N*-(3-oxocyclohexyl)carba-

mate (XIV). Intramolecular cyclization of carbamate (XIV) in the presence of pyrrolidine and $Et_3N$ in $CH_2Cl_2$ affords racemic methyl 4-oxooctahydroindole-1-carboxylate (XV), which is then subjected to chiral chromatographic separation, resulting in the (3a*R*,7a*R*)-enantiomer (XVI). Finally, 1-ethynyl-3-methylbenzene (VII) is stereospecifically added to ketone (XVI) in the presence of *n*-Hex-Li in THF (2). Scheme 1.

**Scheme 1.** Synthesis of Mavoglurant



## BACKGROUND

Glutamate is the principal excitatory neurotransmitter in the brain, and glutamatergic neurotransmission is involved in most aspects of normal brain function, and is often altered in neurological conditions. Glutamate receptors are either ionotropic, or ligand-gated ion channels, or metabotropic receptors. The latter are members of the group C family of G protein-coupled receptors which modify neuronal and glial excitability through G protein subunits acting on membrane ion channels and second messengers. Metabotropic glutamate (mGlu) receptor ligands have been evaluated for their potential in treating numerous disorders, including Alzheimer's disease, Parkinson's disease, anxiety, depression and schizophrenia. The eight subtypes of mGlu receptors have been categorized in three groups based on structure and physiological activity. Group I includes $mGlu_1$ and $mGlu_5$; the primary effect of group I receptor activation is excitatory and can have neurotoxic effects (3-5).

Two conditions in which the $mGlu_5$ receptor has been implicated are fragile X syndrome (FXS) and levodopa-induced dyskinesia (LID) in patients with Parkinson's disease. The most common form of inherited mental retardation, FXS is characterized by mild to severe cognitive impairment, autistic behavior, attention deficit and hyperactivity, hypersensitivity, speech delay and epilepsy. Current treatment of FXS is aimed at alleviating these associated disorders with mood stabilizers, antipsychotics, anticonvulsants, antidepressants, anxiolytics and psychostimulatants. Physical abnormalities are typical of this disease and include long face, prominent ears, flat feet, hyperextensible joints, low muscle tone and macroorchidism in males. Males are generally more severely affected than females. The prevalence is 1 in 4,000 males and 1 in 6,000-8,000 females worldwide (6, 7).

FXS results from expansion of a CGG trinucleotide repeat in the 5′-untranslated region of the fragile X mental retardation 1 (*FMR1*) gene. This leads to reduced expression of the fragile X mental retardation 1 protein (FMRP), an mRNA-binding protein involved in the transport of target mRNAs and the silencing of the translation of target mRNAs during transport. FMRP has also been found to be involved in translational regulation of target mRNAs in synaptosomes after $mGlu_5$ receptor stimulation. Increased mGlu receptor activity has been detected in *Fmr1* knockout mice, which also display behavioral abnormalities consistent with the human phenotype and analogous dendritic abnormalities. It may be that without FMRP, $mGlu_5$ receptor-mediated pathways are not repressed, and excess $mGlu_5$ receptor signaling leads to the characteristics associated with FXS, such as epilepsy, cognitive impairment, developmental delay, increased density of long, thin dendritic spines and loss of motor coordination. The mGlu receptor theory of the FXS phenotype maintains that with activation of group 1 mGlu receptors, mRNAs are translated locally at the synapse and AMPA receptors are internalized. Proteins synthesized in response to activation of mGlu receptors in many brain regions are involved in various brain functions. Lack of the translational repressor FMRP results in elevated protein synthesis and a net loss of AMPA receptors in the postsynaptic membrane. Loss of AMPA receptors results in abnormal synaptic electrophysiological activity and dendritic spine morphology. Evidence supporting the theory comes from experiments with the $mGlu_5$ receptor antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP), which was found to rescue various aspects of FXS in animal models of the condition. This compound has limited utility as a treatment, however, due to its lack of specificity (8-10). As shown in Table I, there are at least three $mGlu_5$ receptor antagonists being actively developed for FXS.

Glutamatergic hyperactivity in the basal ganglia has been noted in LID, leading to the notion that antagonism of glutamatergic transmission could ameliorate the condition. Moreover, high striatal expression of the $mGlu_5$ receptor has been noted, and primates developing hyperkinesia after levodopa administration displayed an increase in the density of the $mGlu_5$ receptor; $mGlu_5$ receptor expression was also enhanced in the post-mortem brains of Parkinson's disease patients with motor complications, and the $mGlu_5$ receptor antagonists MPEP and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) reduced dyskinesias in rodent and primate models of Parkinson's disease (11-13). This offers some promise for a condition which affects many, if not most, Parkinson's disease patients (estimated prevalence ranges from 30% to 80%) treated for an extended period of time with the major therapy for the disease, levodopa. Other treatment approaches, such as altering levodopa doses, formulations and frequency of administration and using dopamine agonists, deep brain stimulation and amantadine, have shown limited efficacy and/or practicality. Drug-induced dyskinesias are associated with reduced quality of life among patients with more severe or predominantly painful dyskinesias (14) (see Table II).

The possibility of treating these conditions with an $mGlu_5$ receptor antagonist is being investigated at different companies, and one of the programs furthest along in the development process is that for

***Table I.*** *Compounds under active development for the treatment of fragile X syndrome (FXS).*

| Phase | Drug name | Mechanism of action | Organization |
|---|---|---|---|
| Preclinical | Ganaxolone | $GABA_A$ receptor modulator | Marinus Pharmaceuticals |
| Phase I | STX-107 | $mGlu_5$ receptor antagonist | Seaside Therapeutics |
| Phase II | RO-4917523 | | Roche |
| Phase II | Donepezil | Acetylcholinesterase inhibitor | Stanford University |
| Phase II/III | Mavoglurant | $mGlu_5$ receptor antagonist | Novartis |
| Phase III | Arbaclofen | $GABA_B$ receptor agonist | Seaside Therapeutics |

Source: Thomson Reuters Integrity™.

***Table II.*** *Compounds under active development for the treatment of dyskinesias associated with Parkinson's disease.*

| Phase | Drug name | Mechanism of action | Organization |
|---|---|---|---|
| Phase I | Naluzotan hydrochloride | 5-$HT_{1A}$ receptor agonists | Proximagen |
| Phase I | Neu-120 | NMDA receptor modulator | Neurim Pharmaceuticals |
| Phase I/II | NP-002 | Nicotinic receptor agonist | Neuraltus |
| Phase II | Dipraglurant | $mGlu_5$ receptor modulator | Addex Pharmaceuticals |
| Phase II | Mavoglurant | $mGlu_5$ receptor antagonist | Novartis |
| Phase II | Fipamezole hydrochloride | $\alpha_2$-Adrenoceptor antagonist | Juvantia, Santhera |

Source: Thomson Reuters Integrity™.

mavoglurant (AFQ-056). Mavoglurant has entered phase II/III development for FXS, for which it has orphan drug designation in the U.S., and phase II development for LID. (Mavoglurant is also in development for chorea in patients with Huntington's disease, although information on this research is scarce. A phase II study in this indication was terminated [15]). Results so far have gone some way to validating the biological evidence that $mGlu_5$ receptor antagonism will have beneficial effects in treating these conditions.

## PRECLINICAL PHARMACOLOGY

Mavoglurant was discovered through optimization of a lead compound identified via high-throughput screening. Studies in vitro showed that the agent noncompetitively inhibited glutamate-induced activation of the human $mGlu_5$ receptor expressed in L($tk^-$) cells with an $IC_{50}$ of 30 nM. The compound was found to bind in the transmembrane domain of the $mGlu_5$ receptor and had no activity at the human $mGlu_1$, $mGlu_2$, $mGlu_4$ and $mGlu_7$ receptors or the human $GABA_B$ receptor, the $P2Y_2$ receptor or when tested against a panel of central nervous system (CNS)-relevant receptors (16).

Mavoglurant was tested in *Fmr1* knockout mice using a prepulse inhibition of startle (PPI) behavioral test to evaluate sensorimotor gating, as heightened sensitivity to sensory stimuli is a common FXS symptom. Mice were injected intraperitoneally (i.p.) with vehicle to measure basal PPI, and then on the same day and 30 minutes prior to the PPI experiment, with mavoglurant 3 mg/kg i.p. PPI was measured using an eye-blink response. Wild-type mice showed an inhibition of startle response of 47% after prepulse, while *Fmr1* knockout mice showed 25% inhibition of the startle response after prepulse. This was rescued after injection of mavoglurant, where *Fmr1* knockout mice demonstrated a 48% inhibition of the startle response after prepulse; inhibition was 53% in wild-type mice treated with mavoglurant. In addition, cultured *Fmr1* knockout hippocampal neurons had elongated spines compared to wild-type neurons; these were shortened by mavoglurant treatment in a concentration-dependent manner. Unexpected results were a decrease in dendritic spine width and an increase in spine density in dissociated hippocampal neurons from *Fmr1* knockout mice (9).

Evidence supporting the exploration of mavoglurant as a treatment for LID was derived from a study in an animal model of Parkinson's disease, the MPTP-lesioned monkey. Six MPTP cynomolgus monkeys were treated repeatedly with a high dose (15-35 mg/kg) of levodopa, leading to increased locomotion and reduced parkinsonian scores, but also inducing dyskinesias. The increase in locomotion and improvement in parkinsonian scores induced by levodopa were not affected by administration of mavoglurant given at doses of 5, 25, 125 or 250 mg/kg, and locomotion and parkinsonian scores were not affected by mavoglurant 25 mg/kg alone. While the dyskinesia scores for the total period of levodopa effect were not significantly decreased by the addition of mavoglurant, the 1-hour peak dyskinesia scores were significantly reduced with mavoglurant 125 and 250 mg/kg. Maximal dyskinesias were also reduced by mavoglurant 25, 125 and 250 mg/kg. It was also found that the administration of mavoglurant 25 mg/kg with a low dose (5.15 mg/kg) of levodopa increased the locomotor activity of the MPTP monkeys compared to administration of either agent separately; improved parkinsonian scores with low-dose levodopa were maintained with low-dose mavoglurant. In these studies, no abnormal behavior was observed with any of the doses of mavoglurant given alone or with levodopa, and plasma mavoglurant concentrations increased with dose (11).

## PHARMACOKINETICS AND METABOLISM

In mice, mavoglurant displayed a short half-life in plasma and in the brain (0.2 hours upon i.v. administration), with levels undetectable 24 hours after oral administration of 30 mg/kg. No accumulation was observed in mice treated for 5 days (9).

## SAFETY

Mavoglurant was compared to placebo in a double-blind, two-treatment, two-period crossover study in 30 male adults with FXS aged 18-35 years. The participants were randomized to receive mavoglurant 50 mg b.i.d. on days 1-4, 100 mg b.i.d. on days 5-8, 150 mg b.i.d. on days 9-20, 100 mg b.i.d. on days 21-24 and 50 mg b.i.d. on days 25-28, followed by placebo or vice versa, separated by a 1-week washout period. Only one serious adverse event occurred (severe pneumothorax), but was not related to the treatment. Fatigue was the most frequently reported adverse event, occurring in seven patients treated with AF-Q056 and in five receiving placebo (8).

Two randomized, double-blind, placebo-controlled, multicenter studies evaluated the effect of mavoglurant on LID. In the first of these phase II trials, 31 patients with moderate to severe LID were assigned mavoglurant or placebo b.i.d., taken 1 hour before levodopa treatment and 1.5 hours before breakfast and the evening meal. Mavoglurant dosing was 25 mg b.i.d. on days 1-4, 50 mg b.i.d.

on days 5-8, 100 mg b.i.d. on days 9-12 and 150 mg b.i.d. on days 13-16. Adverse events, mostly mild to moderate in severity, were reported by all participants in the mavoglurant group and in 11 of 16 given placebo. The most numerous were nervous system, gastrointestinal and psychiatric disorders, with dizziness the most common. Four patients given mavoglurant reported five serious adverse events, including worsening dyskinesia, hyperkinesias, a fall and rhabdomyolysis, with all but the fall suspected to be related to the study medication. Adverse events affected dose titration in six patients (13).

Dosing was the same in the second study, with the exception that patients were downtitrated from day 17 to 20. The 28 study subjects had severe LID. Adverse events were noted in 13 of 14 patients in the mavoglurant group and in 11 of 14 in the placebo cohort. These were again mostly mild to moderate in severity, most often were nervous system, gastrointestinal and psychiatric disorders, and dizziness was the most common. Two serious adverse events (psychotic disorder and worsening dyskinesia) were seen in the cohort receiving mavoglurant during downtitration and were suspected to be related to the study drug. Adverse events affected dose titration in seven patients (13, 17).

## CLINICAL STUDIES

The crossover trial in 30 individuals with FXS found that epigenetic modification of *FMR1* may correlate with the response of patients with FXS to mavoglurant. In the study, mavoglurant did not result in significant improvements versus placebo at the study's primary endpoint, the Aberrant Behavior Checklist-Community Edition (ABC-C) score at day 19 or 20 of treatment. The Repetitive Behavior Scale-Revised (RBS-R) score was significantly improved with mavoglurant versus placebo, however. When the participants were divided according to *FMR1* promoter methylation status, the subpopulation with a fully methylated *FMR1* promoter (n = 7) displayed a significantly improved ABC-C score following mavoglurant therapy versus placebo at day 19 or 20 ($P < 0.001$). This included improvements in stereotypic behavior, hyperactivity and inappropriate speech. Significant improvements were also noted on the Clinical Global Impressions-Improvement (CGI-I), CGI-I efficacy index, RBS-R and visual analog scale (all $P < 0.05$), but not on the Vineland Adaptive Behavior Scale (VABS), in this subpopulation. In participants with partial *FMR1* promoter methylation (n = 18), no significant differences were noted between mavoglurant and placebo treatment on any of these measures. The results suggest that the methylation status of the *FMR1* promoter may be used to predict the response of individuals with FXS to mavoglurant therapy (8).

In the phase II study in 31 patients with moderate to severe LID described above, significant antidyskinetic effects were seen on the Lang–Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS) on days 12 and 16 with mavoglurant compared to placebo. Reductions on day 16 were –4.60 and –1.57, respectively, with mavoglurant and placebo. On the modified Abnormal Involuntary Movement Scale (mAIMS), which measures abnormal movements of the head and neck, significant improvement was seen on days 8, 12 and 16 with mavoglurant. Reductions on day 16 with mavoglurant and placebo were –6.93 and –1.63, respectively. Significant improvement also occurred with the drug on the Unified Parkinson's Disease Rating Scale–part IV (UPDRS-IV) items 32-33, an assessment of dyskinesia duration and severity on days 12 and 16, with reductions on day 16 of –1.99 and –0.82, respectively, with mavoglurant and placebo. No effect on the UPDRS-III assessment of motor function was noted at any time point with mavoglurant. Nine patients reached the target dose of 150 mg b.i.d., while the mean dose given on day 16 was 111.7 mg b.i.d. (13).

Of the patients with severe LID given mavoglurant in the second phase II study, 8 of 14 reached the maximum dose of 150 mg b.i.d. On day 16, significant antidyskinesic effects were seen with mavoglurant on the mAIMS, with reductions of –9.75 and –4.84, respectively, with mavoglurant and placebo, and on the UPDRS-IV items 32-33, with respective reductions of –2.56 and –0.98. Mavoglurant was also superior to placebo, although not significantly so, on the LFADLDS and the UPDRS-III (13, 17).

Three phase II studies of mavoglurant in patients with LID are planned or enrolling patients, and a phase II/III will also begin in February 2012, with completion expected in 2015 (18-21). In addition to a phase I pharmacokinetic, safety and tolerability study of mavoglurant in children with FXS, four phase II/III trials in FXS are planned or are recruiting patients, with results expected from two later this year (22-26).

## SOURCE

Novartis AG (CH).

## DISCLOSURES

The author states no conflicts of interest.

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