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Is There a Path Forward for $mGlu_2$ Positive Allosteric Modulators for the Treatment of Schizophrenia?

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ABSTRACT: Two recent Phase II results show opposing outcomes for the potential of activators of mGlu2 in the treatment of schizophrenia. The first outcome revealed that Eli Lilly's mGlu2/3 agonist, pomaglumetad methionil (LY2140023), failed to meet the primary efficacy end point. The second report showed the mGlu2 positive allosteric modulator (PAM) from Addex (ADX71149) in conjunction with Janssen Research & Development met the primary objectives of safety, tolerability and demonstrated an effect on negative symptoms in patients.

KEYWORDS: *Agonist, $mGlu_{2/3}$, $mGlu_2$, positive allosteric modulator, PAM, Phase II*

Schizophrenia (SZ) is a complex and chronic mental health disease that affects nearly 1% of the total adult population with more than 2 million Americans suffering from this disease a year. Because the disease normally presents itself in early adulthood (late teens/early twenties), the overall cost of this disease is staggering with costs well over $60 billion (based on estimates from 10 years ago).[1] Although the name is derived from the Greek words for split (schizo) and mind (phrene), sufferers do not have split personalities, but suffer from unusual and/or disturbed thoughts, hallucinations, delusions, and lack of emotion and energy. The most prescribed medications for the treatment of SZ are so-called first- and second-generation antipsychotics (atypical antipsychotics) that work as antagonists of the dopamine 2 receptor (D_2 antagonists). However, these compounds continue to be plagued by severe side effects such as significant weight gain and metabolic disorders. Due to these side effects, new and more effective treatments with fewer side effects have been the focus of significant research into this field of treatment.

It has been 15 years since the first reports on the activation of metabotropic glutamate receptors and subsequent reversal of phencyclidine (PCP) induced cognitive deficits and psychosis.[2] From that time, there have been multiple academic and industrial programs dedicated to the glutamate hypothesis of schizophrenia.[3] Arguably the most advanced of these numerous projects is the activation of the Group 2 metabotropic glutamate receptors ($mGlu_{2/3}$). Eli Lilly led the charge in this new area with their $mGlu_{2/3}$ orthosteric agonist LY2140023 (a prodrug of LY404039), which showed efficacy in 2007 in a 4-week phase II trial (Figure 1).[4] Although the efficacy was not as significant as a prototypical atypical Zyprexa, LY2140023 did not produce the weight gain as seen with Zyprexa. Unfortunately, the excitement over this initial phase II study has been buffered with newer results showing either inconclusive results[5] or, more recently, results that are no better than placebo.[6]

The first, inconclusive, result was from the phase II study HBBI comparing LY2140023 with placebo or olanzapine. Although LY2140023, at any dose, was not more efficacious than placebo, the results were considered inconclusive since the active control did not separate from placebo. The study was performed in patients with acutely exacerbated schizophrenia. In this study, LY2140023 monohydrate was well tolerated, though there were four cases of a serious adverse event (convulsion). In the more recent phase II HBBM study, LY2140023 was again tested against placebo and an active control; however, in this study, the active control was risperidone. Two doses were investigated (40 and 80 mg) in both an overall population and a predefined genetic subpopulation. In this study, LY2140023 (now known as pomaglumated methionil) did not show efficacy compared to placebo in either population or dose. However, the positive control risperidone was efficacious (compared to placebo) in both populations.[6] Despite these results, Eli Lilly continues to study LY2140023 in a number of clinical trials as potential adjunct therapies, with new results expected in Spring 2013 of a Phase III trial.

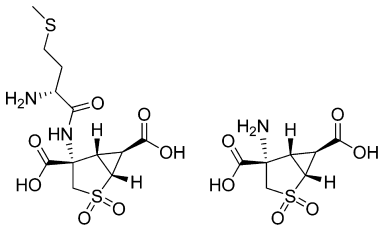

Figure 1. Structures of the Eli Lilly $mGlu_{2/3}$ agonist (LY040039) and prodrug (LY2140023).

Contrasting to the orthosteric $mGlu_{2/3}$ agonist, there has been significant effort in finding novel allosteric modulators of $mGlu_2$. These positive allosteric modulators (PAMs) potentially provide more subtype selective molecules than traditional orthosteric agonists, and since the PAMs only act in the presence of endogenous ligands, they are thought to overcome

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the receptor desensitization that often plagues orthosteric agonists. The most advanced $mGlu_2$ PAM is from Addex, in partnership with Janssen R&D, ADX71149. Although the structure of ADX71149 has yet to be released, Addex has published extensively on two separate scaffolds as mGluR2 PAMs: disubstituted pyridine/isoquinolines[7] and imidazo[1,2-*a*]- and triazolo[4,3-*a*]pyridines[8] which were derived from a scaffold hopping campaign (Figure 2). In addition to

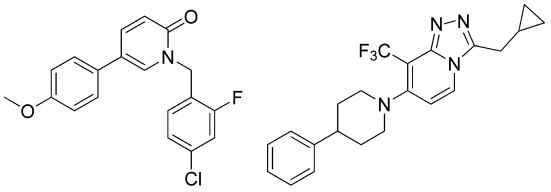

Figure 2. Representative $mGlu_2$ scaffolds from Addex/Janssen in the primary literature.

publications in the primary literature, patent applications have published around these two scaffolds: pyridones[9] and triazolo-[4,3-*a*]pyridines.[10] Although it can be difficult to ascertain information regarding the structure of ADX71149, these publications shed light into medicinal chemistry campaigns for $mGlu_2$ PAMs. Lastly, the most recent publication from these groups disclose an effort to identify potential tracers for positron emission tomography (PET) imaging.[11] The Addex/Janssen groups have disclosed novel chemical matter that have shown excellent efficacy in preclinical models of SZ.

However, and more excitingly, Addex has recently reported a successful Part B of the first-in-patient Phase IIa clinical study of ADX71149 in SZ.[12] The Phase IIa study was separated into two parts which were run concurrently with Part A looking at the safety, tolerability, and efficacy as monotherapy in patients with subacute psychosis and Part B was as adjunctive therapy to antipsychotics. The data that was reported in late 2012 showed that ADX71149 met the primary objectives of safety and tolerability and demonstrated an effect in patients with residual negative symptoms.

This promising data is welcome news for the millions of patients and caregivers that suffer from SZ. However, as was highlighted with LY2140023, this excitement must be tempered with the knowledge that there is a long road to go before ADX71149 or any similar therapeutic is available to the community. Will these positive allosteric modulators succeed where the orthosteric agonists have not? Only time, and more clinical data, will tell. However, with so many pharmaceutical companies fleeing psychiatry as a therapeutic area, it is welcome news that there are those still progressing potential drugs forward for this devastating and not-well-treated disease.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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