ACS Chemical Neuroscience pubs.acs.org/acschemicalneuroscience

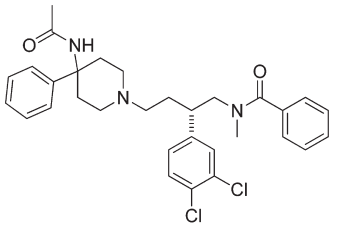
Viewpoint

ACS Chemical Neuroscience Molecule Spotlight on Saredutant

Corey R. Hopkins

Vanderbilt University Medical Center, Department of Pharmacology and Vanderbilt Program in Drug Discovery, Vanderbilt University, Nashville, Tennessee 37232-6600

Abstract



Saredutant®, SR48968
Neurokinin-2 receptor antagonist

Saredutant (SR48968), a potentially novel treatment option for major depressive disorders (MDD) and generalized anxiety disorder (GAD), is a drug from Sanofi-Aventis currently in phase III clinical trials. MDD is a common mental disorder that affects 121 million people worldwide, nearly 4% of the adult population (www.who.int/mental_health/management/depression/definition/en/). MDD continues to be one of the leading causes of disability with more than three quarters of the diagnosed cases having effective treatments available (www.who.int/mental_health/management/depression/definition/en/). However, even though MDD affects a large portion of the population, effective treatment options with low incidence of adverse events remain a major concern for the pharmaceutical industry. Adverse events (GI side effects1, weight gain, somnolence/insomnia, etc. (Demyttenaere, K. (2003) Risk factors and predictors of compliance in depression. *Eur. Neuropshychopharm. 13*, S69−S75)) from the typical treatments remain the major reason for premature stopping or poor compliance of treatment. New treatments to the market must bear in mind these adverse events, and the pharmaceutical industry is currently looking for drugs with new mechanisms of action and those that are better tolerated.

Keywords: Saredutant, MDD, major depressive disorders, neurokinin-2 receptor antagonist

Saredutant (SR48968) is a new and novel treatment option for major depressive disorder. Saredutant, a potentially novel treatment option for major depressive disorders (MDD) and generalized anxiety disorder (GAD), is a drug from Sanofi-Aventis currently in phase III clinical trials. MDD is a common mental disorder that affects 121 million people worldwide, nearly 4% of the adult population (*1*). It is one of the leading causes of disability worldwide, with fewer than 25% of those affected having access to effective treatments (*1*). However, even though MDD affects a large portion of the population, effective treatment options with low incidence of adverse events remains a major concern for the pharmaceutical industry. Adverse events from the typical treatments remain the major reason for premature stopping or poor compliance of treatment. Those events include: GI side effects, somnolence/insomnia, sexual dysfunction and weight gain (*2*). Thus due to these effects, there remains a need for new drugs with new mechanisms of action and those that are better tolerated.

Saredutant is a novel, non-SSRI treatment for MDD that is designed to block the effects of neurokinin A at the G-protein coupled receptor (GPCR) neurokinin-2 (NK2). A number of potential therapeutic indications of NK2 antagonism have been proposed, namely, asthma, inflammatory bowel disease, pain, and psychiatric disorders (*3*). Its mechanism of action is different from those of antidepressants currently marketed, and thus, the adverse events are expected to be lessened. In 2007, Sanofi-Aventis reported that four phase III studies had been completed (two studies statistically significant and two studies not statistically significant versus placebo) evaluating that Saredutant in the treatment of MDD demonstrated a statistically significant overall efficacy versus placebo on depressive symptoms (*4*). In addition, in early 2008, the results of two phase III clinical trials were released (*5*). In the INDIGO study, the drug did not reach significance versus placebo (same for the comparator). The pooled results demonstrated a positive short-term benefit for patients suffering from MDD as measured by the HAM-D score. However, as expected, Saredutant lacks

Received Date: June 16, 2010
Accepted Date: June 21, 2010
Published on Web Date: October 20, 2010

DOI: 10.1021/cn100061r | *ACS Chem. Neurosci.* (2010), *1*, 653–654

the side effects frequently observed with current therapies. Saredutant showed significantly less nausea, absence of sexual dysfunction (CSFQ total score), absence of insomnia, and absence of somnolence when compared to other drugs (*6*). In another study (MAGENTA), evaluating the maintenance of the effects of Saredutant in MDD confirmed the product's good long-term safety profile (*7*). However, the study also showed that the relapse was not significantly reduced compared to that of the placebo when patients who had responded to the drug after 3 months had their treatment extended to 12 months (*7*). As with the INDIGO study, short-term analysis revealed a benefit for patients with MDD on the basis of the HAM-D scale.

With these mixed results from two studies, the regulatory approval for Saredutant will hinge on the outcomes of two additional ongoing trials assessing the product in combination with selective SSRI escitalopram (Lexapro) and paroxetine (Paxil). These results are expected to be completed in the first half of 2009 (*7*). In a May 2009 letter to shareholders, Sanofi-Aventis announced that it will discontinue the development of Saredutant (SR48968) (*8*).

References

1. See www.who.int/mental_health/management/depression/definition/en/.

2. Demyttenaere, K. (2003) Risk factors and predictors of compliance in depression. *Eur. Neuropshychopharm. 13*, S69–S75.

3. Longmore, J., Hill, R. G., and Hargreaves, R. J. (1997) Neurokinin-receptor antagonists: pharmacological tools and therapeutic drugs. *Can. J. Physiol. Pharmacol. 75*, 612–621.

4. Sanofi-Aventis press release, February 13, 2007.

5. Sanofi-Aventis press release, April 30, 2008.

6. Sanofi-Aventis, R & D Meeting, September 17th, 2007.

7. Sanofi-Aventis press release, July 31, 2008.

8. Sanofi-Aventis letter to stockholders, May 18, 2009.

DOI: 10.1021/cn100061r | *ACS Chem. Neurosci.* (2010), *1*, 653–654